VOLUME 16 *Boston Number* NUMBER 4

THE MEDICAL CLINICS OF NORTH AMERICA

JANUARY, 1933

PHILADELPHIA AND LONDON
W B SAUNDERS COMPANY

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CLINIC OF DR GEORGE R MINOT

FROM THE THORNDIKE MEMORIAL LABORATORY, SECOND AND FOURTH MEDICAL SERVICES (HARVARD), BOSTON CITY HOSPITAL, AND THE DEPARTMENT OF MEDICINE OF THE HARVARD MEDICAL SCHOOL

THREE CASES OF CHRONIC DIETARY DEFICIENCY

The Features are (1) Chronic Fatigue, (2) Anemia, (3) Prolonged Coagulation Time of the Blood

ILL health dependent upon chronic dietary deficiencies is common although in civilized countries the fully developed syndromes of vitamin deficiencies are relatively rare The borderline states of nutritional insufficiency need better recognition, as does the fact that apparently satisfactory nutrition does not mean optimal nutrition Chronic departure from the optimum diet, even if slight, can produce ill health when operative over a long period of time and especially if combined with digestive disorders or other adverse factors Temporary alterations in the diet do not lead to deficient states In studying patients a detailed dietary history will often indicate how individuals may be made better by changes in their diets This history must be sought for with care and is often difficult to obtain One must attempt to learn the amount and kind of food the patient has eaten daily during his lifetime, noting any changes that have occurred for any prolonged period of time. Experience will show that there are many difficulties in obtaining such information and one must be well acquainted with the detailed dietary habits of many sorts of individuals to be in a

position to evaluate adequately a dietary history The patient may be unable to furnish the history with any degree of reliability If questions are asked rapidly and offhand answers are accepted many errors will be made Cross questioning and rechecking the information is important For example, if one asks, "Do you have meat daily?", the reply may be, "Yes, we always have meat" That reply might be accepted as indicating the patient ate a liberal amount of meat, but sometimes, after cross questioning, it is learned that the meat was on the table with regularity, but that the patient ate very little or none! One must not be satisfied with the dietary history until knowledge has been obtained regarding the amount and kind of food taken, including its method of preparation

The 3 cases I shall present to you illustrate some states of nutritional deficiency, the value of a careful dietary history, and the benefits derived from a proper diet for the given individual

The *first case* is that of a married woman of fifty years of age She tells us that she believes that nothing can be done for her as she has suffered from kidney disease for five years Five years ago she sought the advice of a physician because she felt unduly fatigued and suffered from mild constipation He told her she had Bright's disease, and should never again eat meat or eggs and rarely poultry She has followed this advice faithfully Fish and milk were permitted but she excluded the latter and very seldom has eaten fish

During the past five years the patient has suffered from progressive muscular weakness and abnormal fatigue, mental irritability and depression, taking more and more a pessimistic view of any matter with which she is concerned She says, "I have totally forgotten how to smile!" At no time in the past ten years has the patient been under mental or physical strain sufficient in any way to account for her becoming progressively abnormally fatigued Constipation has not been troublesome in recent years Sometimes, especially in hot weather, she has noticed that her ankles and feet were slightly swollen, and occasionally she has experienced a mild generalized headache. She always feels languid

It is noted upon complete *physical examination* that she has a slightly muddy complexion and is a trifle pale The heart is perhaps slightly enlarged but the sounds are of good quality and regular The systolic and diastolic blood pressures fluctuate between 140 and 160 and 80 and 90 mm of mercury, respectively No other findings of consequence were detected

The urine persistently has contained a slight amount of albumin with occasionally a rare hyaline cast in the sediment Renal function studies of various sorts are interpreted as indicating a slight degree of kidney impair-

ment There is evidence of slight simple anemia with the hemoglobin 78 per cent of normal and the red blood cells 4 500 000 per cubic millimeter

Cross questioning has brought forth the fact that for many years she has not cared for red meat and seldom ate such food more than twice a week, so that it pleased her to be told five years ago that she should not eat this sort of food, and has thus not had any meat in recent years She was accustomed to eat 2 to 4 eggs a day prior to five years ago but otherwise during the past five years her diet has been little different than for the past ten or more years. It has been composed essentially as follows

Breakfast Fruit usually an orange.

Two slices (whole loaf) of toast with 2 butter balls and often a table spoonful of honey or marmalade.

Usually 2 or 3 slices of bacon

Coffee with 2 lumps of sugar but never with cream

In the *middle of the morning* she has been apt to eat a small piece of cake or 3 or 4 simple white (5 Gm) crackers and in summer to drink a bottle of ginger ale.

Luncheon Vegetable soup usually, but sometimes a meat soup (1 cup)

About three times a week fish is eaten but she never takes more than about 75 Gm

A large helping of vegetable salad with French or mayonnaise dressing (often 1½ tablespoonfuls) has been eaten with regularity Cheese is disliked but she has eaten a little about once a week. Four simple crackers or a slice of bread and butter have been eaten usually with the salad

Dessert has consisted of one of the following

(1) Fruit—often one banana

(2) A pudding (large helping) made with some sort of flour much sugar and sometimes a little apple or a few raisins or prunes.

(3) A gelatin dessert.

(4) Ice cream, rarely

In the afternoon a piece of cake and a cup of tea with sugar and lemon have been taken frequently

Dinner This meal has been very similar to luncheon except for fish which has not been taken Poultry however not over 70 Gm has been eaten twice and rarely three times a week. She usually had at this meal one or another sort of cereal (a small dish full) with much (90–150 cc.) molasses or maple syrup but very rarely with milk or cream. She has been apt to eat distinctly more green vegetables than at luncheon and not infrequently had three large helpings Each evening she ate a medium sized potato and sometimes macaroni Dessert has been of the sort she has had at luncheon

Before going to bed she usually has eaten a dish of cooked fruit which was advised owing to constipation

Curiously enough she does not like and thus has not eaten various sorts of shell beans and nuts plant foods which are relatively rich in protein.

It is evident that this patient's diet for a long time has been deficient in protein, but sufficient in its caloric content since she

has maintained for the past five years her body weight at about 130 pounds, which is suitable for her height

Individuals partaking for a long time of a diet deficient in protein may experience exactly the sort of symptoms this patient has had including the slight swelling of the feet and ankles Great reduction of protein with chiefly concentrated carbohydrate food in the diet may lead to the condition known as edema disease (prison dropsy, war edema, etc)

This patient has perhaps a slight degree of chronic nephritis with slight hypertension, but it is clearly evident that damage to her cardiovascular and renal system is certainly slight At the time this patient was told she had "Bright's disease" her symptoms were of the sort that can be attributed to protein deficiency of at least five years' standing and now five years later her symptoms, which have increased greatly, can be attributed very largely to that condition

There was a time not so many years ago when restriction of nitrogen intake was considered desirable to lessen the burden of the kidney in excreting nitrogenous products It is now, however, well recognized that the individual with damaged kidneys is no exception to the rule that the protein requirements of the body must be met Indeed, it is possible that some type of persistently faulty diet which does not supply the organ with optimal nutrition may enhance or even possibly cause chronic kidney degeneration Thus curtailment of protein below optimal requirements is undesirable in health and in chronic disease Furthermore, in certain types of chronic heart and kidney disease there occurs a considerable loss of protein from the body by way of the urine so that the protein requirements of such individuals may be even greater than normal

The treatment of this patient consists in prescribing an adequate well-balanced diet and reassuring her that no harm will arise from eating plenty of food containing protein in liberal amounts

Three months later this patient appeared before the class again

There was considerable difficulty in getting her to eat properly but after rather tedious conversations and paying

detailed attention, with consumption of much time, to the patient's anxieties and discomforts, she did eat well within a month and took regularly an excellent diet The significant changes in her diet are indicated by the following statements She ate red muscle meat, about 80 Gm , four times a week and cooked calves' liver, 100 Gm , six times a week This latter food was prescribed because of its being unusually rich in complete proteins At the other meals each week, except breakfast, she had from 70 to 80 Gm of poultry or, rarely, fish At breakfast she took two eggs

She now has a good color, looks very much better and says, "I feel splendidly and stronger than I have for a great many years" "I do not get tired easily and, curiously enough, I seem to enjoy my present diet" She can now smile, and her outlook on life has changed very much for the better The anemia has vanished The urine on several recent examinations has shown either no, or very little, albumin and no casts Recent renal function tests may be interpreted as normal The blood pressure remains at the same level as formerly It is probable that the amount of albumin in the urine previously and the slightly abnormal renal function recorded were much more dependent upon a functional impairment of the kidney associated with her defective nutrition than upon chronic nephritis The case illustrates, of course, the needless suffering for years of a woman unfortunately advised who might have had good health during the past decade if she had partaken of a proper diet

The *second case* is that of a woman twenty six years of age. The salient aspects are as follows For the past year she has noted always tired and lacks pep frequently constipated with occasionally large soft foul smelling stools not due to cathartics often troubled with intestinal gas is more nervous than formerly never feels well She has lost 5 pounds of body weight in a year but her weight is not abnormal

The patient looks rather pale and tired but complete *physical examination* brings forth no further positive facts for our present consideration The blood examination shows that simple anemia exists with hemoglobin 56 per cent of normal and the red blood cells 4,300 000 per cubic millimeter There is no history of abnormal blood loss infection or the like which might be the cause of the anemia The gastric analysis shows slight hypochlorhydria Numerous other laboratory and special examinations are negative

She has explained that she has told her story to 5 physicians and has been given various "tonics," advised to rest more, to have a long vacation, and to take mineral oil and agar agar She has been unable to take a long vacation, but she has given up many evening pleasures so that she now is in bed nine hours at night rather than only seven and a half hours She also rests on Sundays rather than "playing hard all that day as formerly" She considers that this increased amount of rest has caused her to feel better but she remains far from well Critical inquiry regarding her daily régime indicates her work is tedious and exacting She lives three quarters of an hour trolley ride from the store where she works all day in artificial light, seldom walks over one half a mile a day, and takes no other exercise After she returns from work she has many duties to perform at home

Her dietary habits are clearly abnormal Like so many young women, who sooner or later suffer in one way or another from the habit, she has eaten for years only a very scant breakfast This meal consists of a cup of clear coffee, a slice of toast with butter and, rarely, jam About five hours later she seldom has more than twenty-five minutes to go out and obtain her noonday meal This state of affairs has existed for two years and has resulted in her eating for luncheon typically as follows A meat (usually chicken or ham) sandwich, a piece of cake, an ice cream soda and often a large amount of chocolate ($\frac{1}{4}$ pound) or candy (7 to 15 pieces) In the late afternoon she has usually eaten 2 slices of bread with a little butter and sometimes a cup of tea At night she is tired and although she often feels hungry, soon after she begins to eat she finds her appetite sense has vanished This has caused her, she says, to eat her food fast in order "to get it down" During the past two years she has eaten for her evening meal approximately as described below in contrast to the excellent well-balanced meal of former years It has "tired her to eat red meat" so she seldom took any and if she did she was apt to chew it, but not swallow more than the juice She usually has eaten 2 eggs or a small piece of poultry or fish She has been prone to help herself liberally to vegetables but she almost always leaves a considerable amount of such food on her plate, so that she has eaten approximately only a small potato and about a tablespoonful of green vegetables or, rarely, salad She usually enjoys several slices of bread or pieces of cake with butter and dessert which has often been a large

helping of a sweet pudding, very rarely made with fruit Ice cream and pie have been taken about once a week

The complete data indicate that the indigestion is functional and a part of it can be attributed to carbohydrate intestinal indigestion as told by her symptoms and by the fact that the stools are strongly acid and form on standing much more gas than normal

It is obvious that this young woman has not had a proper diet for at least two years and has eaten her food too fast Her diet has been distinctly sparse in green vegetables and fruit, has been relatively rich in concentrated carbohydrate food and sugar and the protein and iron content has been rather low She has had a difficult daily régime which alone might be responsible for her chronic fatigue The carbohydrate intestinal indigestion certainly contributes to her symptomatology as does the simple hypochromic anemia Simple hypochromic anemia, especially in women, is prone to develop following an improper diet and more readily when disorder of the gastro intestinal tract exists, particularly gastric achlorhydria. The important rôle that altered gastric secretion and faulty intestinal absorption or abnormal function may play in the production of hypochromic anemia is not for discussion here Iron in proper form and amount can correct such anemia, but, of course, a suitable diet should be prescribed for each case Diet alone, probably largely because of its iron content, may correct this sort of anemia especially when it is slight and the gastro-intestinal function is not severely altered as in this patient's case When diet causes this sort of anemia to vanish it does so much more slowly than when appropriate amounts of iron are given, probably because of a relatively small intake of iron in the first instance and the consumption of large amounts when the inorganic element is fed

Four months later this patient was brought again before the class

This woman was not given iron in order to demonstrate the effect of food alone Her work has not been changed but arrangements were made so that she has had no duties at home, rested one-half hour before her evening meal and has had an hour

off duty at noon She has taken with considerable regularity a one and one-half mile walk each evening and has continued to be in bed nine hours at night

Her diet was changed gradually as it was impossible for her to eat at once the most suitable food for her Much persuasion and detailed supervision were necessary All grossly sweet foods, including cake, were omitted and the quantity of concentrated carbohydrate food somewhat reduced and given especially in the form of dextrinated material, such as zwieback, on account of the carbohydrate intestinal indigestion She has eaten for breakfast one egg, a dish of hot whole wheat cereal and cream (60 cc , 20 per cent), 3 pieces of zwieback with 20 Gm of butter and a large helping of fruit The other meals were well balanced and included fruit (often cooked), usually red meat, sometimes poultry and rarely fish, liberal helpings of tender green vegetables and often a salad Before she ate entirely satisfactorily, but after the grossly sweet food had been omitted, the type of concentrated carbohydrate largely changed, and the amount reduced for three weeks, the signs and symptoms of carbohydrate intestinal indigestion vanished Likewise she felt distinctly better, but at this time the anemia remained of the same degree This illustrates a common observation that distinct improvement due to diet may be observed long before the patient is well Now that she has continued faithfully and intelligently the régime under frequent medical supervision for four months she looks well, has gained 7 pounds of body weight, and the amount of hemoglobin and number and character of the red blood cells are normal

This type of case is common and successful therapeutic results will only be obtained by insisting on a suitable régime of life and the partaking of food properly and an optimal diet for the individual patient

The *third case* illustrates that nutritional defects associated with chronic deficiency of the caloric content of the diet may lead to prolonged coagulation time of the blood The case will be presented briefly

The patient is a boy, seventeen years old, who is thin and distinctly undernourished He presents a desiccated appearance with some pallor

and poor muscular development The boy does not consider that he is sick and wonders why his relatives and the doctors want to bother him although he admits he cannot play as hard or do as much as his friends His tonsils are enlarged and chronically infected No other significant findings were noted on physical examination He has been advised that his tonsils should be removed

He tells us that a year ago following removal of a tooth bleeding lasted for two days and that he has had nosebleeds frequently in the past two years.

The coagulation time of the venous blood is abnormally long as determined by several tests on the average 1 25 cc. of blood in a glass tube 1 cm in diameter clotted in twenty four minutes instead of normally in from eight to fifteen minutes The clot was firm and retracted normally The blood platelets occur in normal numbers although the bleeding time is a trifle prolonged There is no history of hemophilia or hemorrhagic disease in any of his many relatives and he has had no joint symptoms of any sort which are so common in hemophilia due to hemorrhage into the joint cavity The differential diagnosis of hemorrhagic disorders is not for discussion here.

The undernutrition can readily be explained by his dietary habits He has for years been a fussy and finicky eater with a dislike for a great many foods. No effort of consequence has ever been made to have him eat properly His diet has been for a long time low in its caloric content and abnormal in various other ways being sparse in foods rich in vitamins calcium and complete proteins and fats The only green vegetables he will eat are corn and onions He never takes cream and only about 3 ounces of milk a day which is put upon a prepared ready to-serve cereal He does not like butter and takes very little. Fruits also are disliked except oranges and grapefruit, but he seldom eats them He has eaten little meat never fish and has chicken about 3 times a week. Sausages bacon and salt beef are taken several times a week. Eggs only if scrambled are eaten about twice a week. Crackers biscuits, potato some cereals and rice, doughnuts griddle cakes and many sorts of pies cake and nuts have been eaten freely He does not care for candy or sugar He has many grotesque ideas about food and its preparation and at times has decided he would eat only potato oranges, and chicken and several times his parents have allowed him to have only these three foods for two to three weeks at a time When such was the case the total amount of food eaten did not apparently contain a sufficient number of calories for health

Exactly what sort of dietary defect may alter the coagulation time of the blood is not definitely known, but in certain instances prolongation of the coagulation time apparently develops as the result of a defective diet, which may have an insufficient caloric content Not only may individuals like this boy have prolongation of the coagulation time of their blood, thus favoring abnormal bleeding from injury, but the abnormal nutritional state appears to alter the condition of the tissues in such a way that capillary

closure is imperfect, which also favors hemorrhage and more so, of course, if the blood does not clot properly A proper diet for a sufficient time can correct such defects, but diet will not in any significant way affect the blood of hemophiliacs

Surgical operation upon individuals with such conditions as this boy has may cause an abnormal amount of bleeding This is especially true when the site of the operation is in the nose or throat where the absence of soft parts permits easy bleeding and where capillary closure is relatively difficult Under such circumstances, however, abnormal bleeding does not always occur even when the coagulation time of the blood is somewhat prolonged If the throat operation is completed without undue hemorrhage, the danger from hemorrhage is not passed because sometimes from two to seven days later, or when an exudate loosens, severe and prolonged hemorrhage may take place, presumably owing in part to defective capillary closure with blood which clots with some difficulty Thus, before this boy has his tonsils removed, it is wise to first improve his nutritional state and, indeed, it is evident that he will be in all respects a much happier and healthier young man if he will eat properly

Three months later this patient again appeared before the class

The boy was placed in a hospital for three weeks where he was trained to eat properly, although it required much time and careful attention on the part of nurses and physicians He has been given a diet rich in foods containing liberal quantities of protein, fat, and calcium and an abundance of vitamins He also has taken 2 to 6 teaspoonfuls of cod liver oil each day For the past two months he has eaten his food with relish and enjoys all sorts of fruits, cream, meats, and many foods he used to consider "he could not possibly eat " He has rested three to four times for half an hour each day During the past three months he has gained 11 pounds of body weight He looks ever so much better and admits that he feels much stronger The coagulation time of his blood has been normal when tested on several occasions during the past month, if he had had hemophilia this would not have occurred

Simple local treatment has been applied to his tonsils during the past three months but they remain obviously infected and will be removed very soon without fear of hemorrhage

The abnormal diet taken by these 3 patients has been relatively easy to detect, but in concluding I want you to realize that less abnormal diets taken over a long time may be responsible, wholly or in part, for ill health which may be reflected by only minor symptoms and a slight lack of the normal sense of well being

CLINIC OF DR HENRY A CHRISTIAN

PETER BENT BRIGHAM HOSPITAL

CONGENITAL AND ACQUIRED AORTIC STENOSIS IN ADULTS

IN the last few years several papers[1] have renewed interest in aortic stenosis unassociated with lesion of other cardiac valves The frequency of massive calcification in association with acquired aortic stenosis, its occurrence almost solely in males, the long duration of its physical signs, particularly the murmur, the usual development of symptoms of decompensation from it relatively late in life and the great hypertrophy of the heart, when finally cardiac failure is fatal, all have been stressed in these papers In a considerable number of patients with acquired aortic stenosis, a rheumatic history may be obtained, and rheumatism seems to be a fairly definitely determined etiology However, not infrequently no history suggestive of antecedent rheumatic fever in any of its manifestations can be obtained, and when this happens, especially in younger adults, the question naturally is raised whether the lesion is an acquired one or one of congenital origin Such a question arose with 2 patients studied in my clinic at the Peter Bent Brigham Hospital, whose histories now will be presented

Case I.—E W W P B B H Med No 38 766 male age twenty-seven years, was admitted to the hospital March 30 1931 complaining of breathlessness of three months duration

Family History.—Negative.

[1] Margolis, H M Zielleissen F O, and Barnes A B Calcareous Aortic Valvular Disease, Amer Heart Hour 6 349 1931 Christian Henry A Aortic Stenosis with Calcification of the Cusps, a Distinct Clinical Entity Jour Amer Med Assoc 97 156 1931 and Aortic Stenosis with Calcification a Clinic, Internat Clinics 3 51 (41st series) 1931

Past History—Negative except for measles, whooping cough and tonsillitis in childhood with tonsillectomy in 1908

Present Illness—In 1906, at the age of three, the patient had pneumonia, followed by chronic bronchitis and "heart disease" He has been told that until this time his heart was quite normal and that his physician felt that the heart lesion caused by the pneumonia would heal in the course of time In 1920, at the age of sixteen, the patient again had pneumonia after which, for about one month, he had symptoms very similar to that of the later present illness, except that there was no edema of the ankles He remained in bed for one month, during which time he was quite ill, and for two months more of convalescence During this time there was some medication, the character of which is unknown Patient feels that it was not digitalis In 1928, three years before admission, there was an attack of grippe with cough productive of a small amount of yellowish sputum accompanied by head cold, fever and a generalized aching of his bones and muscles There was some slight dyspnea and palpitation but no swelling of the ankles After several weeks in bed he recovered completely

In the interval between this and the latest attack the patient has entered into strenuous sports, such as tennis, football, canoeing, etc, without apparent ill effects and without unusual dyspnea or fatigue

In November, 1930, five months before admission, the patient caught a severe cold while watching a football game There was nasal obstruction and discharge, questionable fever and an unproductive cough There was a generalized soreness of his bones and muscles and a pain over his heart, radiating to the right lower chest, above and at the sides, especially on coughing This was somewhat sharp in character though not severe Since then there has been a chronic cough, productive of a small amount of yellowish sputum, which on one occasion was slightly blood streaked There has been a generalized muscle soreness and with this a progressive dyspnea ever since

Since about March 4th he has felt very badly On climbing about half of one flight of stairs he has become very dyspneic, somewhat dizzy, and there has been "a slight pull on the heart, but not quite a pain" For the past three months he has used two pillows at night for the past three weeks, that is, since March 7th, two pillows have been insufficient, and he has not been able to lie down without extreme dyspnea and coughing

Six weeks before admission, *i e*, about February 15th, his ankles began to swell, especially at night, and for the next two weeks he took Doan's kidney pills, 2 pills t i d This relieved the swelling somewhat so that he was able to get his shoes on, but on stopping this medication, his ankles became more swollen again

March 21st or 22d, about ten days before admission, he had a cough, productive of a yellowish sputum which at one time was blood streaked, and his temperature was 103 to 104 F for three days His physician made a diagnosis of grippe Since then there has been a rather sharp pain starting at the heart region and radiating to the right lower chest and over the liver, which is worse on deep inspiration Two days before admission this pain was very much worse and was present all the time Since then it has quieted

down somewhat This pain was relieved by cough mixture At no time have there been hemoptyses or night sweats

Physical examination shows a somewhat emaciated patient sitting up in bed in considerable respiratory distress

Physical examination is essentially negative except as described below

Heart—R. B D 4 7 cm , L. B D 13.5 cm from midsternal line There is a slight systolic thrill at the apex and a coarse marked systolic thrill in the aortic region felt from the bottom of the second rib to the fifth rib along the right sternal margin but not felt to the left of the sternum At the apex region there is a fairly soft blowing systolic murmur which increases in intensity and roughness as one approaches the basal region and is loudest in the aortic area In the aortic area there is a very slight very early diastolic murmur

Peripheral Vessels—Radial pulses are synchronous and equal regular in rhythm rate 88 of plateau type and very small in excursion Vessel walls are palpable

Blood Pressure—Systolic 85 diastolic 60

Lungs are resonant throughout and breath sounds are vesicular in character Tactile fremitus and spoken and whispered voice are unchanged There are numerous crackling râles in the bases of both lungs as high as the angle of the scapula and in both axillae.

Abdomen is well developed and symmetrical without visible peristalsis There is a marked epigastric pulsation synchronous with cardiac systole. The entire abdomen is somewhat tender most markedly along the right costal margin There are no herniae or evidence of fluid

Liver is palpable three fingerbreadths below the right costal margin Surface and edge are smooth and somewhat tender

Extremities—There is very marked pitting edema of the ankles, extending up as far as the knee The fingers show slight curving of the nails and slight clubbing with cyanosis and some softening of the tissues at the root of the nails

While in the hospital the patient had no fever and his Wassermann reaction and blood culture were both negative. Urine was normal Hemoglobin 75 per cent red blood cells 5 040 000 white blood cells 11 400

x Ray at a distance of 7 feet showed fluid in the left base of the lung obscuring part of the heart outline. As far as seen, the heart appeared enlarged chiefly to the left Measurements showed a transverse diameter of the heart of 13 4 cm in a chest whose internal diameter was 25 8 cm.

This patient was subsequently admitted to the Massachusetts General Hospital where he died [1] An autopsy showed a very large heart weighing 500 Gm with marked hypertrophy and dilatation of all chambers The aortic valve showed an extreme

[1] This case was presented and discussed among Case Records of the Massachusetts General Hospital edited by Dr R. C Cabot. See report in New England Jour Med 206 906 1932

degree of stenosis There was marked calcification of all the cusps In addition to the long-standing chronic stenosis there was a fresh acute endocarditis on the aortic valve There was no very definite lesion of any of the other valves The lungs showed very definite bronchiectasis in the left lower lobe

Case II.—A C, P B B H Med No 40,585, male, age forty years, was admitted to the hospital February 26, 1932, with a complaint of weakness and pain across the back of two months' duration and abdominal pain of two weeks' duration

Family history is negative

Past History —Patient denies any past illnesses

Present Illness —Patient feels that he was perfectly well until two months ago He then noticed that, when he exerted himself excessively, he had an aching pain across the back of the shoulders This pain would last for only about two minutes He also noticed at this time that he was more tired than previously His wife says he was slightly short of breath One month ago the patient went to his physician who told him to go home and to stay in bed He gave the patient some green pills (digitalis), telling him to take three per day He has taken three every day since then The backache has been present while the patient was in bed, not keeping him awake During the last two weeks the patient has had lower abdominal pains with bowel movements twice a day, watery in character There has been no nausea, vomiting or yellow vision His physician gave him bismuth subcarbonate, but his pains continued, and he was referred to this hospital for diagnosis

Physical examination shows a fairly well-developed, poorly nourished man, lying in bed with no apparent acute distress Physical examination in general is negative except as described below

Heart —The patient has a distinct but not marked cardiac hypertrophy L B D is 14 cm from midsternal line, part of which position seems to be due to a heart dropped away from the chest wall as there is distinct zone of pulmonary resonance to the left of the sternum and no dulness can be percussed to the right There is a very loud systolic murmur heard at any point over the precordium but loudest at the base and particularly over the aortic area In the aortic area there is a rough, systolic thrill easily felt from the aortic region up to the first right interspace There is also an early diastolic murmur of moderate intensity and lasting half-way through diastole, heard best along the left sternal margin at the level of the third and fifth interspaces The latter murmur is just heard at the apex There is no late diastolic murmur

Peripheral Vessels —Radials and brachials are cordlike and of small caliber Radial pulses are equal, small and of plateau type, rate 84

Blood Pressure —Systolic 112, diastolic 100

Lungs show fine crepitant râles at both bases in the posterior axillary lines Left diaphragm does not descend on deep inspiration Otherwise the lungs are normal on percussion and auscultation Tactile fremitus, voice fremitus and breath sounds are normal

Abdomen is well developed symmetrical with no pulsations nor visible peristalsis There is slight tenderness in the lower abdomen No masses can be felt The abdomen is resonant throughout without spasm hernias or fluid

Liver is normal to percussion edge not felt

Spleen —Tip can be felt two fingerbreadths below the costal margin

Extremities —Legs show no edema There is well marked clubbing of the fingers with cyanosis of the nails and softening and increased elasticity of the nail beds. A similar but less well marked condition is present in the toes

While in the hospital patient showed a fever with rises averaging about 101 F His Wassermann reaction was negative Blood culture was negative Urine was negative. Hemoglobin 94 per cent red blood cells 6 110 000 white blood cells 12 650

Stereo x ray of the chest showed the lungs to be clear and the heart to be enlarged to the left with a rounded prominent left ventricle and widened tortuous aorta Fluoroscopy and fast films of the heart fail to show calcification of the valves

Patient died on March 6th and autopsy showed the following condition of the heart The heart weighs 605 Gm The epicardial fat is normal in amount The mitral valve admits the tips of three fingers whereas the tricuspid admits the tips of four fingers. The heart is full of partly clotted blood but no antemortem thrombi are found The pulmonic and tricuspid valves are translucent throughout and are a grayish white in color The mitral valve presents the same appearance except that it shows a small amount of slightly nodular thickening of the free edge and a few small atheromatous plaques in it The aortic valve cusps are quite free from each other but all of them are greatly thickened and toughened One-half cm below the cusps of the aortic valve there is a fibrous band running almost completely around the aortic ring and protruding into the lumen as a shelf about 3 mm. broad The cusps of the valve are heavily overgrown with an irregular granular grayish yellow mass of vegetation which extends up into the aorta for a distance of 2 cm These vegetations are for the most part quite firm and adherent although some of them are friable The coronary orifices are not involved The chordae tendinae are grayish white in color and show no evidence of thickening or shortening The papillary muscles are greatly hypertrophied The myocardium is a brownish red in color and presents the usual fine striations. The fibrous tissue seems to be scanty The coronary arteries are opened and are found to present a small amount of atheroma formation. The atheromatous plaques are scattered varying in size up to 3 mm in diameter The upper third of the descending branch of the left coronary arteries contain about a dozen pin point granular masses which are grayish yellow in color and appear to be portions of the vegetation on the aortic valve In addition the perforating branch of this coronary artery is completely occluded by a firm gray and purple antemortem thrombus There are no signs of infarction The heart shows evidence of congenital subaortic stenosis with a superimposed subacute vegetative endocarditis.

Lungs show congestion and edema but no evidences of bronchiectasis or other chronic lesion

In each of these patients cardiac physical signs indicated aortic stenosis as the dominant cardiac lesion In each there was a diastolic murmur in the basal region of the heart as evidence of a coexistent aortic regurgitation, but the murmur was not conspicuous, and the low pulse pressure and absence of a Corrigan pulse indicated that the aortic regurgitation was of very minor significance Neither patient had any physical signs of other valves being involved than the aortic In neither patient was there any past illness suggestive of rheumatic fever as an etiologic factor Wassermann reactions did not indicate syphilis Apparently these patients were suffering from the effects of aortic stenosis of unknown etiology in a heart otherwise normal but for hypertrophy

Case I was diagnosed as having a cardiac lesion at the age of three, at the age of sixteen cardiac decompensation was present to reappear at twenty-four and again at twenty-seven to persist for seven or eight months until his death, each time cardiac disturbance followed respiratory tract infection Case II appears to have had no cardiac symptoms until less than three months before his death at the age of forty

Case I showed a slight degree of clubbing of the fingers, in Case II fingers were markedly clubbed, and the toes showed moderate clubbing This feature aroused much interest in our clinical study of these patients It was realized that clubbed fingers are associated usually with congenital heart lesions or with chronic pulmonary lesions and that anoxemia is the explanation usually given for their occurrence, slighter degrees of clubbing were known to be a frequent accompaniment of subacute bacterial endocarditis

In neither one of these patients did physical signs or *x*-ray reveal any chronic pulmonary lesion to account for clubbing of the fingers, although Case I had a history of repeated respiratory tract infection beginning with pneumonia at three Congenital cardiac lesion was considered in each as a possible cause of the clubbing of the fingers, and this was supported in Case I by the diagnosis of a cardiac lesion at the age of three, but in neither were there physical signs of any form of chronic cardiac lesion

other than aortic stenosis with very slight aortic regurgitation In neither had there been a history of cyanosis, and no cyanosis was noted in them while in the hospital

While under observation in my clinic Case I had no evidence of bacterial endocarditis, while Case II definitely was so diagnosed However, the degree of clubbing of fingers and toes in Case II was far in excess of that observed to result from bacterial endocarditis Hence we had no satisfactory demonstrable cause to offer in explanation of the observed clubbing of the fingers

In *x* ray study of each patient, no evidence of calcification of the heart valves was observed In Case I it is fair to say that no particular effort was made by the *x*-ray department to demonstrate calcification, and fluoroscopic examination was made by an assistant roentgenologist In Case II special technic and particular attention was directed toward demonstrating calcification in the region of the aortic valves, but none was demonstrable It was realized, however, that only in some of our patients with aortic stenosis of the calcification type has it been possible to demonstrate roentgenologically during life the presence of calcification

Autopsy, performed at another hospital, in Case I revealed aortic stenosis with calcification and a recent bacterial endocarditis The lungs showed evidence of bronchiectasis in the left lower lobe of the lung, which in *x* ray studies made at the Peter Bent Brigham Hospital during life was probably largely obscured by fluid at the left base and by the enlarged heart The bronchiectasis in Case I probably was the cause of the moderate degree of clubbing of the fingers.

Autopsy on Case II showed the typical lesion of the subaortic stenosis, a congenital lesion In addition there was an extensive bacterial endocarditis of the aortic valve The lungs showed no chronic lesion The only explanation to offer for the marked clubbing of fingers and toes is the congenital cardiac lesion which was present. However, it is difficult to understand the exact mechanism of the formation of clubbed fingers in a patient with a congenital form of aortic stenosis, when clubbing of any appreciable degree is absent in acquired cardiac lesions and particu-

ularly in aortic stenosis with calcification, which differs in almost no respect so far as effect on the circulation is concerned from a congenital type of aortic stenosis such as was found in Case II Certainly there seems no reason to suppose that anoxemia was more in evidence in the one than in the other

However, it would seem justifiable to make a diagnosis of congenital heart lesion, when fingers are markedly clubbed, provided no chronic pulmonary lesion can be demonstrated At any rate this reasoning would have led to recognition of the form of lesion present in Case II and established an entirely correct diagnosis, since the physical signs fully justified a positive diagnosis of aortic stenosis, and as the congenital form of aortic stenosis so often is the subaortic one, it might have been called subaortic stenosis It is to be remembered, however, as shown by Case I, that chronic pulmonary lesions cannot be excluded by a negative x-ray examination, unless special methods are used to make certain that the lung behind the heart is normal, methods which cannot be carried out satisfactorily during the stage of severe cardiac decompensation nor when fluid is present in the pleural space I have had other clinical experience to justify attaching great significance to well-developed clubbing of the fingers as indicative of a congenital heart lesion in the absence of evidence of chronic pulmonary lesion, even though there is nothing clinically found suggestive of the existence of chronic anoxemia In fact, such clinical experience makes one skeptical of the essential importance of anoxemia in the mechanism of the development of clubbed fingers

Summary and Conclusions—Two cases are reported, both in adult life, with physical signs of aortic stenosis, in one of which a marked degree of clubbing of the fingers should have been a diagnostic sign that the variety of stenosis in this case was of the congenital type and not the acquired type, as was present in the second patient, in whom moderate clubbing of the fingers was caused by bronchiectasis Well-clubbed fingers, in the absence of evidence of chronic pulmonary lesion, should be considered as justifying the diagnosis that a clinically demonstrated cardiac lesion is of congenital type

CLINIC OF DR J H MEANS

FROM THE THYROID CLINIC OF THE MASSACHUSETTS GENERAL HOSPITAL

DIAGNOSIS AND TREATMENT OF THE SEVERAL TYPES OF GOITER

FROM the accounts that some of my patients give me of the advice they have received about swellings in their thyroids I am led to believe that some confusion still exists in the professional mind concerning the diagnosis and treatment of the several types of goiter It seems reasonable therefore to devote this clinic to an attempt to clarify some of these matters

Patients with thyroid swellings usually ask at once, "Doctor have I a goiter?" To answer this question the doctor must himself know what the term implies As commonly used today any enlargement of the thyroid may properly be called a goiter, and the processes which may enlarge the gland are obviously various Hyperplasia of the parenchyma is one, excessive storage of colloid is another Simple congestion may cause acute swelling or the thyroid may become the seat of inflammation, acute or chronic, with exudative or proliferative changes Degenerative phenomena, for example cyst formation, fibrosis, and calcification, are frequently found and the thyroid may give rise to a considerable variety of new growths, both benign and malignant

It is not sufficient for the doctor to reply, "Yes, you have a goiter" He must be able also to offer some suggestion of its variety and of the type of mischief which it may produce

One may divide the symptomatology of goiters into local and hormonic. Local symptoms are those caused by pressure of the enlarging thyroid on neighboring structures, or those such

as pain and tenderness caused by inflammatory changes within the gland itself The pressure symptoms in order of their frequency we have found to be hoarseness or aphonia from recurrent laryngeal nerve involvement, sensation of choking from compression or dislocation of the trachea, dysphagia from encroachment upon the esophagus and finally stridor from tracheal occlusion The symptoms of hyper- or hypofunction of the gland I presume are sufficiently familiar as to require no comment A possible third category of symptoms and signs might be mentioned, namely constitutional other than hormonic This would include fever and leukocytosis in acute inflammations, and cachexias due to cancerous growths of the gland

When the doctor becomes aware of the presence of a goiter he must examine it locally and also search for those three categories of symptoms He must discover how long it has been present and the details of its rate of growth In short, given a goiter the doctor must seek to answer four questions Is there change in thyroid function? Is there evidence of pressure? Of malignancy? Or of inflammation?

The local examination of the gland is highly important On inspection its contour and symmetry can often be detected Nodules may sometimes be easily seen during the act of swallowing On palpation one seeks to learn chiefly contour and consistency Of course one should also be receptive to any vascular thrills which may be elicited Whether the gland is uniformly enlarged or irregular, lumpy, or as we usually call it nodular, is of paramount interest, also the consistency of the whole gland if the enlargement is diffuse, and of nodules if they be present Often the pathology can be accurately foretold solely from the experience of careful palpation For example, simple colloid swelling gives a soft, floppy goiter, the borders of which merge with surrounding soft parts so that the outlines of the gland cannot be sharply demarcated The diffusely hyperplastic goiter of Graves' disease, on the other hand, is firm, elastic and easily mapped out It often pulsates or thrills Graves aptly likened it to engorged erectile tissue Stony hard thyroids strongly suggest either chronic thyroiditis or malignant goiter

In either of these the goiter may become adherent to neighboring tissue Sometimes the goiter in chronic exophthalmic goiter gets markedly fibrosed and almost as hard as in malignancy Tenderness of the thyroid is evidence strongly in favor of acute inflammation

The nature of nodules is more difficult to discover, in fact it can only be determined with accuracy by histologic examination The softer nodules are often merely encapsulated or isolated areas of colloid tissue A simple colloid goiter, smooth, and soft to start with, as it ages may become irregular and lumpy just as one's countenance becomes wrinkled with age On section, however, the histology may be uniformly simple excess of colloid storage Other soft nodules turn out to be cysts containing fluid Firmer nodules may be benign adenomas or even early malignancy Very hard nodules always are strongly suggestive of malignant disease although sometimes they turn out to be calcified benign adenomas

All these things the doctor must bear in mind as he feels the neck of his patient with a goiter, and the local findings will give him a hint as to what else is likely to be present The simple colloid gland should be accompanied by little symptomatology If symptoms are present they are probably not due to the goiter The diffuse, firm, elastic gland indicates that thyrotoxicosis is probably present The nodular gland suggests that it may be but not of necessity Nodular goiters particularly malignant ones and those of chronic thyroiditis are the most likely to give pressure Goiters which are low seated, dipping beneath the sternum also squeeze the neck structures more readily than those more highly located This reminds me to say that on palpation one should always seek the lower border and try to gain some information as to whether the gland extends into the thorax

The treatment will depend upon the kind of goiter which after such study the doctor decides he is dealing with We believe in our clinic that three conditions represent absolute indications for early operation—the presence of thyrotoxicosis, of pressure symptoms, or the suspicion of malignancy Another type of

indication very rarely met with is drainage of suppuration within the gland Simple colloid glands require no treatment unless for cosmetic reasons Nodular glands present the greatest problem If none of the three factors just mentioned are present, operation if ordered is for cosmetic reasons or prophylaxis The likelihood of thyrotoxicosis to develop late is not a very urgent reason for operating on a nodular goiter No great harm results if operation is not done until the hyperfunction has actually begun Some people will live their three score years and ten and carry their nodular goiters to their graves without ever having had any thyrotoxicosis The prevention of cancer is of greater moment Of the actual incidence of thyroid cancer we know very little It is undoubtedly more likely to occur in persons with preexisting nodular goiters but it may come on out of an absolutely clear sky in a person with no known previous thyroid disease The proportion of malignant goiters to total goiters of all kinds removed at operation has been found in various clinics to be all the way from 1 to 5 per cent In our own clinic the malignant thyroid cases constitute 1 5 per cent of all thyroid cases whether operated or not It is a remarkable fact that the hyperplastic goiter of Graves' disease has practically never been found to become the seat of cancer We know of no patient who has had Graves' disease who has later had thyroid cancer

This leaves us, however, still in a quandary as to what to say to the patients with nodular goiter producing neither pressure or thyrotoxicosis Some surgeons advise all such patients if they are over twenty-five years of age to have their goiters out On the ground that this constitutes important prophylaxis the policy is defensible although throwing a fear of cancer into such patients as a means of inducing them to consent to operation, in my opinion, is not It is quite possible to obtain consent on other grounds without destroying the peace of mind as mention of cancer always does

My own belief is that patients with nodular goiters past thirty should be advised to have subtotal thyroidectomies done Patients under thirty may be simply watched In any case of

nodular goiter increase in size of nodules or increase in their density, should be considered indication for operation, and even when but a single nodule is present we believe the operation should be subtotal thyroidectomy If one nodule is present the chances are strong that others may be hidden away in the substance of the gland so that even the surgeon cannot discover them If this is so, then removal of one nodule constitutes no very promising cancer prophylaxis Also in toxic goiter and in goiters operated because they are producing pressure, subtotal thyroidectomy is preferable to less extensive resection In other words, in our clinic we are coming to the policy that if one decides upon the removal of a goiter at all it should be upon a subtotal removal

I propose now to show some cases illustrating the ways in which we seek to recognize the type of goiter and then to plan the treatment, with special reference to hyperfunction, pressure, malignancy, and inflammation

First let us consider the case of Mary G (Lab No 9261) an Italian girl of fifteen who was seen in our thyroid clinic first on July 10 1931 She had had a swelling in her neck for a year together with some hoarseness a loss of 5 pounds in six months and occasional choking sensations for three months. Aside from these there were no symptoms.

She showed no eye signs or tremor Her thyroid was slightly and symmetrically enlarged It was slightly irregular and firmer than the usual colloid goiter It was easily mapped out. A bruit was audible over the entire gland The basal metabolism was +2 It was decided that it was probably colloid goiter and that hyperfunction was not present but my colleague Dr Lerman was much impressed with the feel of the gland which seemed more like hyperplasia than simple colloid swelling

The patient was watched for a couple of months and during this time the metabolism fluctuated as shown in the chart. She also gradually became somewhat irritable cried easily and felt the heat more than usual

The picture at this time suggested thyrotoxicosis but was not complete enough to make that diagnosis with finality It was decided to test her reaction to iodine as a means of getting further diagnostic data On September 3 1932 she was started on Liq Iod Comp m x per day In the course of a fortnight her metabolism fell from a level of +12 to one of −15 a total of 27 points and coincidentally her symptoms vanished and the goiter became harder Iodine was then omitted (September 23d) and promptly the metabolism rose again reaching +12 on October 21st. The symptoms returned. It was decided that the obvious response to iodine and return of thyrotoxicosis when it was omitted was sufficient evidence to war

rant a diagnosis of Graves' disease and she therefore was admitted to the hospital on November 5th for operation She was reiodinized by means of saturated solution of potassium iodide m vi per day The response as shown in the chart was quite like the first

On November 18th she had a subtotal thyroidectomy by Dr A W Allen The gland at operation appeared to be that of typical hyperplasia and later the histologic examination showed it to be quite characteristic of Graves' disease

She has been followed ever since As will be noted in the chart for a time the basal metabolic rate without iodine assumed a low level but associated with this were no symptoms of myxedema The extreme low metabolic level was temporary and without medication she finally assumed a level only slightly below the lower limit of standard

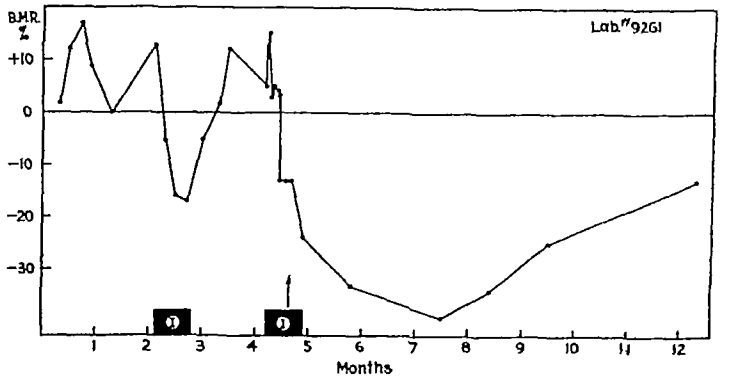

Fig 156 —Metabolic rate in case of Mary G Periods during which iodine was given are marked by I The arrow indicates the time of operation

Ordinarily the diagnosis of Graves' disease is simplicity itself In this case it was not This case teaches us the importance of local examination of the goiter and also that of the diagnostic use of iodine When this girl was first seen, Dr Lerman suspected the correct diagnosis on the basis of the feel of the gland alone Subsequent events showed that his reasoning was correct

The diagnostic use of iodine is beautifully illustrated The two down swings of the basal metabolism in response to iodine and the up swing when its administration was stopped constitute pathognomonic evidence of Graves' disease This girl was thyrotoxic with a metabolic rate barely above standard because her normal basal is somewhat below standard It is the speed and magnitude of the fall in rate when iodine is given, not its absolute level, that is important

In the diagnosis of doubtful cases, watchful waiting may be mentioned also If Graves' disease is developing it will sooner or later declare itself beyond all possible misunderstanding However, the use of iodine is a prompter way of proving the diagnosis than the method of watchful waiting This case illustrates the way in which the question, obscure at first—is thyrotoxicosis present?—finally was answered

Let us consider next the case of Mr F (Lab No 10 609) age sixty nine years who was admitted to the hospital on July 13 1932 with the presenting symptom of dysphagia He had had a goiter chiefly right sided for ten years This had remained stationary in size and produced no symptoms of any description until six months before entry when it began to grow rapidly Along with this growth there appeared some dyspnea and palpitation on exertion He also experienced some anorexia increased nervousness and sweating and a tremor made its appearance. The most troublesome symptom however was dysphagia which began six weeks before entry and steadily increased in severity It became impossible for him to swallow any solid food and for a month he had had nothing but liquids The act of deglutition actually caused pain. In spite of these symptoms he had continued to work. He had lost 10 to 15 pounds in the past year

Examination showed him to be a generally healthy appearing man without eye signs but with goiter and slight tremor The whole thyroid was involved in a marked and fairly symmetrical enlargement. It was of generally firm consistency and easily mapped out and numerous very hard nodules were scattered through its substance. These varied in diameter from 1 to 5 cm There was no evidence that the gland extended beneath the sternum or that it was adherent to surrounding tissues No suggestion of hyper (other than tremor) or hypofunction was obtained by physical examination

The basal metabolism on two successive days was +13 and +2

The x rays which are reproduced in Figs 157 and 158 showed in the anterior posterior view a definite substernal shadow which displaced the esophagus to the right and in the lateral view a slight pressure defect on the posterior border of the trachea together with scattered areas of calcification within the shadow cast by the goiter Barium examination of the esophaguas showed some retention in the pyriform sinus.

One can say at once that we are here dealing with nodular goiter producing pressure. Subtotal thyroidectomy is indicated on that score alone. Although in the history there were certain symptoms that might be due to thyrotoxicosis the absence of objective evidence (other than slight tremor) and the normal basal metabolism makes the existence of hyperfunction unlikely although as the preceding case taught us this last could be said with absolute finality only after the effect of iodine had been tested.

From the fact that dysphagia was here the first pressure symptom to develop and since it is usually the last we concluded that the thyroid must

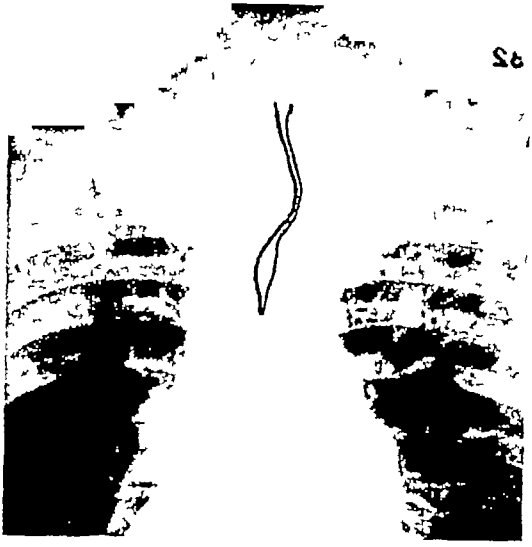

Fig 157 —Roentgenogram of the chest in the case of Mr F The esophagus contains barium which could be made out easily in the original film but is lost in the reduction The shadow of the esophagus has been carefully outlined in ink The lateral displacement thus becomes clearly evident

Fig 158 —Lateral view of the neck in the case of Mr F The shadow of the posterior extension of the goiter is clearly visible behind the trachea Within the shadow and also in front of the trachea several calcified regions can be distinguished

have recently invaded the region behind the trachea, and cautioned the surgeon to explore this region especially thoroughly

The chief point to be settled was whether the goiter was malignant The story of goiter of ten years without change in size, then rapid growth in the past six months, coupled with the finding of stony hard nodules in the gland, we believed could hardly be explained on any basis but malignancy developing in preexisting nodular goiter

At operation July 18, 1932, by Dr Richard H Miller it turned out to be a good sized goiter almost completely encircling the trachea and pressing on the esophagus It was delivered without much difficulty and all removed with the exception of a little on each side posteriorly

The microscopical examination of the tissue removed showed in most places the typical structure of colloid goiter The acini were large and dilated with inactive epithelium There was fairly extensive fibrosis A few areas of old hemorrhage with hemosiderin deposits were found In a few areas small collections of small cells without definite glandular structure were discovered These suggested fairly active growth but no mitoses were seen No blood vessel invasion was observed The pathologist did not believe that there was any evidence upon which a diagnosis of malignancy could be made.

The operation gave immediate and complete relief to the dysphagia On October 19 1932 however when the patient was seen for follow up this symptom had begun to return No regrowth could be found to explain it

The case is of interest because of our inability to confirm the diagnosis of malignancy anatomically The areas of active growth could have been purely benign adenomatous tissue The stony hardness can be accounted for by calcification However, he is still a carcinoma suspect and therefore is being kept under careful observation

The case illustrates further the importance of *x* ray in studying the effects of pressure Flattening and displacement of the trachea is often seen in either the anterior posterior or lateral views and after barium, as here, displacement or narrowing of the esophagus For the demonstration of substernal extension we are also largely dependent on the *x* ray

I should like to present to you now the facts in the case of Mrs. O., a patient seen six years ago in consultation with Dr W J Mixter She was a physician s wife of fifty six who gave the story that until six weeks before the time we saw her (November 16 1926) she had been splendidly well At that time she discovered for herself a slight fullness in the region of the upper right pole of the thyroid This steadily increased in size and extended toward the middle of the neck. It had been neither painful red nor tender at any time On October 17th she was started on iodine and this was continued for three weeks. It had no apparent beneficial effect indeed a progressively

increasing difficulty in breathing made its appearance with the beginning of the iodine therapy and also a loud, paroxysmal, unproductive cough Orthopnea began about October 20th and was very marked at the end of a fortnight Slight hoarseness and dysphagia had been present since October 17th

There were no symptoms of disturbed thyroid function Indeed, there were no constitutional symptoms at all

She stated that in 1917 and again in 1924 physicians had suspected her of having a mild degree of hypothyroidism and had prescribed thyroid On each of these occasions she took the drug for a short time only and was able to detect no effect

A year before the present illness began she was again given thyroid by a dermatologist for a dry scaly eruption of the face Under thyroid this disappeared but she had continued with ½ grain a day ever since

Examination showed a woman with marked respiratory distress of the type characteristic of tracheal obstruction (stridor) Her voice was harsh and talking difficult

The entire thyroid was moderately enlarged and stony hard It definitely extended beneath the sternum It was without thrill and bruit, very fixed but *smooth* The *skin* was *not* adherent It was *nontender* The trachea seemed pushed to the left

The lungs showed scattered, dry râles throughout and slight dulness over the entire right back

In other respects the physical examination seemed unimportant

x-Ray examination showed the shadow of the tumor in the neck extending to the lower border of the clavicle It was not intrathoracic The trachea was pushed to the left The lung fields were clear and the heart shadow not remarkable Laryngoscopy showed no vocal cord palsy but there was a distinct inbulging of the left tracheal wall causing obstruction

It seemed clear that this woman had a rapidly growing cancer of the thyroid and would soon be strangled Dr Mixter operated on November 19, 1926, with the primary object of relieving pressure All that he could do was dissect out a portion of the neoplasm directly over the trachea All the tissues of the neck were edematous and firmly bound together However, the procedure in large measure relieved the tracheal stenosis

Histologic examination of the tissues removed showed an extremely cellular tumor infiltrating and almost completely replacing the gland substance It was made up of rather large atypical cells with irregular nuclei and acidophyllic, occasionally vacuolated cytoplasm There was a definite peripheral cell membrane Mitoses were very numerous There was no doubt in the mind of the pathologist that the cells were epithelial in origin and the tumor one of very high malignancy—carcinoma simplex

A course of postoperative x-ray treatment was decided upon and two thirds of an erythema dose was given in divided sittings between November 23d and 30th At the completion of this series the mass had almost disappeared and the symptoms were gone

Seen on December 21st she appeared and claimed to feel well The mass had practically disappeared

On January 22, 1927, she was sent back to the hospital having within a

fortnight had a return of her dyspnea in even more severe form than before The growth in the neck had returned A second course of x ray treatment was given in the same way as before Upon completion of this on January 26th a film of the chest showed a mass in the upper mediastinum about two thirds the size of the heart extending both to the left and right of the mid line quite dense and with lobulated and sharply defined margins. It was continuous with the shadow in the neck.

This second course of x ray had but little good effect The goiter and dyspnea persisted On February 9th a third course was begun this time directed lower over the upper sternal region instead of the neck area. No improvement was apparent A film on March 11th showed the mediastinal mass unchanged A fourth course of treatment therefore was given between March 11th and 14th The swelling in the neck, however continued to grow and the dyspnea to increase

On April 6th Dr Mixter saw her at her home in the country The mass in the neck was greatly interfering with respiration There was considerable swelling above the left clavicle and a wide area of substernal dulness.

On April 8th she died No autopsy was obtained

This case represents fulminating thyroid cancer in a woman without known previous goiter, the symptomatology of which is solely that of pressure. It illustrates the inefficacy of treatment and the hopelessness of prophylaxis of this particular type of malignant goiter Fortunately this type is distinctly less frequent than those of less high degree of malignancy arising in preexisting goiter when radical cure or relatively satisfactory amelioration is often possible

The next case, that of Miss Z (Lab No 10 822) a school girl of seventeen also represents the acute onset of symptoms blamable on the thyroid in a person without known previous goiter but of a very different nature.

The symptoms which caused her to come to the hospital on September 24 1932 came abruptly out of a clear sky three days before During the evening she was at work in the school library when she suddenly had a pain in the right side of her neck and a few moments later discovered a swelling there. She went home and in an hour there was a mass as big as a hen's egg in the anterior right neck, painful and tender She went to bed and had several shaking chills. She began to cough and had a feeling as though her wind were being shut off The following day the mass began to decrease in size but remained tender It hurt to swallow

On the day of entry she had a mouth temperature of 102 F and a pulse of 115 The right lobe of the thyroid was found swollen to a size of 3 to 4 cm in diameter It was smooth soft and very tender The left lobe was just palpable. It was not tender The whole neck felt hot. There was neither thrill nor bruit Extension of the neck was painful so was swallow

ing In other respects the physical examination was negative The white blood cell count was 20,400 The basal metabolic rate determined on September 29th was −10 per cent

Here then we have local manifestations which are clearly those of acute local inflammation, pain, swelling, tenderness and heat, combined with the constitutional phenomena of acute infection, chills, fever, and leukocytosis There is no evidence of disturbed thyroid function but there is a suggestion of pressure in the cough and sensation of suffocation

It is a classic picture of acute inflammatory goiter, that is to say acute thyroiditis, unquestionably infectious but by a totally unknown organism and through a totally unknown portal of entry

In the hospital she was treated simply with rest in bed, forced fluids, and ice to her neck In forty-eight hours she defervesced completely and the swelling and tenderness rapidly declined She was discharged on September 29th

She was seen again on October 8, 1932 She felt completely well The entire thyroid was just palpable and soft save for a discreet nodule about 2 cm in diameter in the right lobe There was no tenderness anywhere The basal metabolic rate was −7

In view of these findings after recovery it is reasonable to suppose that the original inflammatory process had been confined chiefly or entirely to the nodule

The prognosis here is excellent There is no important likelihood of recurrent chronic thyroiditis Of course later her nodular goiter may require removal but the single nodule in a girl of seventeen, producing no symptoms, according to our views does not in itself demand resection

These 4 cases, I believe, selected from a large amount of material will serve to illustrate the principles involved in answering the questions—"what kind of a goiter is it and what should be done about it?" Practically every principle of importance in diagnosis or treatment is raised by these cases, the single exception being the recognition and treatment of thyroid hypofunction

CLINIC OF DRS ELLIOTT P JOSLIN, HOWARD F ROOT, PRISCILLA WHITE, ALEXANDER MARBLE, AND MISS HAZEL M HUNT

NEW ENGLAND DEACONESS HOSPITAL

DIABETIC COMA

Contents

Introduction—Ten years ago we recognized that diabetic coma was preventable and yet we do not prevent it It is surely high time for this to be done In the better hospitals diabetic coma ceased to originate before the discovery of insulin, but it remained for Gottschalk[1] to demonstrate that it also can be abolished in the home In the City of Stettin with its 270,000 inhabitants Gottschalk found that there were 14 coma admissions to the hospital in 1926 and 1927, but as a result of a

diabetic campaign, the number was reduced to one in 1928 and none during 1929 and 1930 This was accomplished by the systematic education of the diabetics in the hospital in the practical treatment of their disease and of their family doctors If patients did not have a family doctor, an effort was made to put them in touch with one Literature, talks in medical societies and extension courses were provided A careful follow-up of all cases who had been in hospitals was undertaken with insistence that they keep in close contact with their own physician and through him all treatment was carried out This was stressed Provision was also made for social assistance through nursing, supplies of food, and of insulin Admissions for diabetic coma fell to zero If coma can be stopped in Stettin, why not stop it in other cities as well?

At the moment we do not know the yearly admissions for diabetic coma to all the Boston Hospitals, but at the New England Deaconess Hospital on our own service the admissions per month have trebled since 1923 to 1925 During this period it is true the number of diabetics we have treated has increased and thus the opportunities for coma have been multiplied, but on the other hand the percentage of new cases to the cases which have originated in our own clientele has remained constant at 1 to 2

In Boston and its neighborhood accessible to the hospital there are probably between 3000 and 5000 diabetics, so that the problem is a larger one than in Stettin, but Gottschalk's work in Stettin is a challenge When a patient develops diabetic coma, and much more if he dies of diabetic coma, someone is to blame

Definition —In order to have a definite standard, only those cases in which the plasma CO_2 combining power was 20 volumes per cent or below have been included in these clinics * It is recognized that some patients are nearly unconscious when the

* In compiling data for the present series of cases, the question arose as to whether only cases with a CO_2 combining power of 15 volumes per cent or lower should be included However this did not seem quite fair since in a consideration of the entire group of 221 cases, 5 out of a total of 29 fatal cases would be excluded

CO_2 value is above 20 and other cases may be quite alert when the CO_2 is far below 20 volumes per cent The variability of clinical symptoms and signs is great Classification into precoma and coma without strict regard for chemical standards hardly seems helpful, since it allows so much variation in clinical judgment. We know that whenever ketosis has progressed to the point of lowering the plasma CO combining power to 20 volumes per cent, unless energetic treatment is given, the danger of the development of fatal coma is great There is another clinical reason for choosing this particular value as the dividing point Before the discovery of insulin, recoveries from coma when the plasma CO_2 combining power was above 20 volumes per cent were not uncommon, whereas recoveries when this value was below 20 volumes per cent were extremely rare Thus when we select cases in such a group for discussion we choose those in which except for insulin the outlook is almost hopeless

Clinical Material—To the 179 instances of coma previously reported by us* in these clinics we now add 42, making a total of 221 attacks of coma in 189 patients for the entire period May, 1923, to November, 1932 Six of the present group appeared in the earlier series

In Table 1 the details of the clinical records of the present series of coma cases are given as a continuation of those in previous series In Table 2 all series of coma cases treated by us are compared

The average ages of the patients treated for coma in our former groups of cases (see Table 2) were nearly identical, varying between 31 6 and 29 1 years, but the present 42 cases averaged only 26 1 years. There was no very young or very old patient in the present series, the extremes being six and fifty-seven years Parenthetically we might add that our oldest patient to recover from coma, Case No 6770, still does well Her coma came on at the age of seventy three years when she had had diabetes three years At present she is seventy five and active Undoubtedly the lower average age in the present series of cases accounts in considerable measure for the minimal mortality of 5 per cent

TABLE 1

Forty-two Consecutive Cases of Diabetic Coma

Case No	Age at coma years	Duration of diabetes years	Date	Clinical data: Respiration	Clinical data: Mental condition	Blood: Sugar, per cent: Day 1	Sugar: Day 2	Sugar: Day 3	Plasma CO_2 combining power, volumes per cent: Day 1	Day 2	Day 3	Nonprotein nitrogen, mg per 100 cc.: Day 1	Day 2	Day 3	Urine: At entrance: Diacetic acid	Sugar per cent.	Sugar free after entrance, hours	Insulin. Units: Day 1	Day 2	Day 3	Comment and result
			1931																		
2856*	19 6	9 5	Aug 29	Kussmaul	Conscious	0 56		0 32	16			35			+++	5 6	7	240	65	65	
8802	16 1	1 6	Sept 8	Kussmaul	Conscious	0 46	0 06	0 12	6	34		29			+++	5 2	12	375	45	35	
10502	53 1	6 5	Sept 24	Kussmaul	Unconscious	0 67	0 06		7	31		44			+++	3 5	17	450	45	42	
5776	17 2	4 9	Oct 10	Kussmaul	Conscious	0 13	0 16		12	23					+	0 5		44	40	40	
9233*	26 0	1 4	Oct 19	Normal	Conscious	0 48	0 07		19	37			27		++	4 0	7	50	48	48	
8647	15 9	1 9	Oct 21	Normal	Conscious	0 24	0 12		14	25		41	37		++	2 5		46	32	32	
10550	12 0	0 8	Nov 3	Kussmaul	Drowsy	0 32		0 22	13			29			+++	4 2	10	100	20	24	
5932	18 4	4 7	Nov 7	Kussmaul	Drowsy	0 71	0 08		9			37			+++	6 0	8	390	45	55	
10021	32 4	0 6	Nov 30	Normal	Conscious	0 28	0 24		20						++	5 3		85	40	39	
8654	31 2	2 3	Dec 3	Kussmaul	Conscious	0 30	0 23		12	21			34		++	3 7	9	200	67	82	
6775	57 4	3 9	Dec 9	Kussmaul	Conscious	0 29	0 19		17			34			0	4 2		45	15		
9717	16 0	1 1	Dec. 6	Kussmaul	Conscious	0 38	0 24	0 31	15	25			37		++++	3 5		280	67	45	Fatal
7311*	27 5	3 3	Dec. 13	Kussmaul	Conscious	0 45	0 07	0 06	16	18		26			++	5 6	11	240	52	40	
10647	6 3	0 3	Dec 17	Kussmaul	Conscious	0 48	0 20		8	28					++	6 2		120	60	45	
7251*	17 3	4 3	Dec 19	Kussmaul	Conscious	0 43			15				39		++	4 2	17	185	75		
7428	55 8	3 9	Dec. 19	Kussmaul	Drowsy	0 65	0 19	0 34	11	33	32				+	1 0	12	300	56	70	
8921	10 8	1 9	Dec 23	Kussmaul	Conscious	0 38	0 06		16	37					++++	4 8		100	44	48	
			1932																		
10743	11 5	2 1	Jan 24	Kussmaul	Drowsy	0 36	0 27	0 14	17									95	26	26	
9831	16 8	1 1	Feb 12	Kussmaul	Conscious	0 34	0 15		11									55	31	40	
10893	23 3	1 8	Mar 7	Kussmaul	Drowsy	0 52	0 15	0 13	7	19		50	67	86	++	4 0	19	250	40	32	
7580	29 8	3 3	Mar 20	Kussmaul	Conscious	0 36	0 19	0 07	20	35			29		++	1 8	23	90	90	65	
10918	8 7	0 0	Mar 31	Kussmaul	Conscious	0 44	0 12	0 23	19				27		+++	4 8		35	10	18	
8435	44 0	4 1	Apr 5	Kussmaul	Unconscious	0 74	0 20	0 03	3	22	25	44	48	37	+	3 9	10	510	220	74	Pulmonary tbc
															++	2 8	16				

11006	19	3	0	5	Apr	12	Kussmaul	Unconscious	0	60	0	09	0	27	2	17		54			++	2	7	7	520	20	50	
3778	16	4	12	2	Apr	12	Kussmaul	Conscious	0	35	0	06			12	31		34			++++	3	8		140	63	59	
10970	42	8	2	5	Apr	14	Kussmaul	Unconscious	0	64	0	13	0	30	8	36					+++	4	0	20	320	10	25	
8741	13	8	2	3	Apr	27	Kussmaul	Unconscious	0	38	0	13			19				43		+++	1	4		285	60	30	
3717	24	4	8	5	May	10	Kussmaul	Conscious	0	42	0	17	0	19	19	26			49		+++	2	1		110	55	31	
11081	47	0	8	1	May	15	Drowsy	Conscious	0	60	0	20			15	29		41			++	4	1	8	175	90	58	
6649	56	5	4	5	June	15	Kussmaul	Conscious	0	37			0	29	13					21	+++	2	0	7	210	52	37	
10460	31	1	2	0	June	18	Kussmaul	Conscious	0	46	0	19	0	27	11	20					+++	3	8	7	121	45	17	
6063	15	0	5	6	June	19	Kussmaul	Conscious	0	48	0	30			4	29			33		++	3	0	8	70	65	59	
11138	41	1	0	0	June	20	Kussmaul	Conscious	0	51	0	29			7	28			36		++++	3	0	9	405	65	35	
7063	18	7	6	6	June	29	Kussmaul	Conscious	0	40	0	22	0	21	9	23	33	32	27		++	2	6	7	210	67	52	
11256	15	5	1	6	Aug	2	Kussmaul	Conscious	0	59					6			61			+	5	0	8	100	33	34	
11257	43	0	1	7	Aug	2	Kussmaul	Drowsy														3+			350			Fatal
7311	28	3	4	1	Sept.	7	Kussmaul	Conscious	0	48	0	10			10	38			29		++	4	6		165	58	36	Appendectomy
11315	9	9	0	1	Sept.	7	Normal	Conscious	0	36	0	15			19	37					++	7	2	10	30	27	36	
5267	47	3	7	4	Sept.	25	Kussmaul	Unconscious	0	37	0	16	0	40	6		27		64		++++	6	0	12	240	20	46	
10945	17	4	1	3	Oct.	1	Kussmaul	Conscious	0	36	0	12	0	19	17	30	49	31	26		++	3	6	7	98	60	52	
8105	13	0	3	0	Oct.	12	Kussmaul	Conscious	0	28	0	04			12					35	+++	4	6	6	100	60	36	
2776	20	0	11	7	Oct.	13	Kussmaul	Unconscious†	0	33	0	12	0	30	6	17		37			++++				510	53	60	In labor

Two or more attacks of coma.
† Under amytal anesthesia.

TABLE 2

DIABETIC COMA

Summary Table—Comparative Study, by Averages, of the Five Series

Series and number of cases	Age at coma years	Duration of D M years	Date	Blood						Urine at entrance		Insulin units			Fatal cases	
				Sugar per cent		Plasma CO_2 combining power, volumes per cent			Nonprotein nitrogen mg per 100 cc	Diacetic acid	Sugar per cent					
				Day		Day			Day			Day			No	Per cent
				1	2	1	2	3	1			1	2	3		
I 24 Cases	31 5 24	2 4 24	May, 1923, to Mar , 1925	0 47 23	0 20 20	15 24	33 20	31 10	47 16	++++ 24	3 3 24	154 24	63 22	58 21	5	21
II 28 Cases	31 6 28	2 8 28	Apr , 1925, to Feb , 1927	0 49 28	0 20 20	14 28	29 20	30 10	46 21	+++ 28	3 4 28	166 28	59 26	49 26	4	14
III 53 Cases	29 1 53	4 0 53	Mar , 1927, to Feb , 1929	0 53 52	0 21 46	13 53	28 37	38 12	60 33	+++ 53	3 1 53	183 53	40 50	39 50	5	9
IV 74 Cases	31 3 74	3 5 74	Feb , 1929, to Sept , 1931	0 49 74	0 20 51	11 73	29 42	35 13	48 52	++ 74	3 7 74	252 74	49 65	41 62	13	18
V 12 Cases	26 1 12	3 5 42	Aug , 1931, to Nov , 1932	0 47 42	0 15 37	12 20	28 28	33 5	37 17	++ 42	3 9 40	201 42	51 41	45 39	2	5

The subfigures indicate the number of determinations upon which the average is computed in each series

In contrast to the last series the distribution of cases according to sex in the present one was more nearly even though females still predominate Eighteen of these patients were males and 23 were females

Prior to the third series beginning March, 1927, the duration of the diabetes at the onset of coma was between two and three years, but since that date it has lengthened to three and four years

Admissions for coma per month have trebled since 1923 to 1925 Beginning with 1 1 per month they now have reached 2 8 per month in the present series This increase has been uniformly progressive We believe this is accounted for by the gradual numerical accession to our own clientele in the decade, and also to the recognition by the public of the interest of the New England Deaconess Hospital in diabetes

The blood sugar averaged 0 47 per cent on the first day, and is thus almost identical with previous series, but on the second day it had fallen to 0 15 per cent in contrast to 0 20 or 0 21 per cent in the other groups, thus indicating better treatment

The plasma CO_2 averaged 12 volumes per cent upon admission in contrast to volumes of 15, 14, 13, and 11 per cent respectively in the other groups *By the third day it had risen to 35 volumes* per cent The acidosis has on the average been more severe as represented by the slightly lower value for CO_2, but the mortality has fallen

The average nonprotein nitrogen was 37 mg per 100 cc, thus making this component normal for the first time in the 5 series Very likely this too was a factor in our low mortality, and thus not to be explained as a result of treatment It is possibly related to the younger average age.

The diacetic acid and percentage of sugar in the urine were as before

Rather less insulin was required—201 units during the first twenty four hours of treatment. It is noteworthy that the insulin given has varied inversely with the level of the CO_2 combining power of the blood plasma in all 5 series of cases We administered insulin not according to the volumes per cent of

carbon dioxide in the blood, rather, the dosage was based first of all upon the general condition of the patient and secondly upon the blood sugar and CO_2 Notwithstanding the fact that no attempt was made upon our part to scale the insulin by the CO_2, the two vary together irrespective of the age, size of the patient, and duration of the disease

The mortality of the present series was the lowest yet, being only 5 per cent, in contrast to that in former groups which reached from 9 to 21 per cent respectively Again we attribute the favorable mortality to the lower age of the patients as much as to any one factor

TABLE 3

VARIATIONS IN SEVERITY OF COMA

Date.	Total cases coma	Plasma CO_2 combining power below 10 volumes per cent	
		No cases	Per cent.
1923–1929	105	17	16
1929–1931	74	34	46
1931–1932	42	14	33

In the present series, 14 or one third of the cases, had on admission a CO_2 combining power of the blood plasma below 10 volumes per cent Despite this high incidence of severe coma, a fatal outcome was seen in only one of these 14 cases, this patient, Case No 11,257, discussed later, entered with bronchopneumonia and had neglected treatment of his diabetes Examination of Table 3 shows that the present series contains fewer cases so far advanced as to have CO_2 values below 10 volumes per cent than the series in 1929 to 1931, but twice as many as were found in the period from 1923 to 1929 The large number of children in the present series may provide the explanation, since they usually are treated earlier owing to closer observation by their parents Another factor of importance is the relatively smaller number of severe complications such as septicemia, carbuncles, and acute pancreatitis

Causes of Death —The mortality of the entire series of 221 cases of coma is 13 1 per cent. To the 27 fatal cases of coma reported in the previous series two are to be added from the present group making a total of 29 in 221 coma admissions in

189 patients Both of these recent cases came to autopsy Case No 11,257 had bronchopneumonia, and Case No 6775 had a coronary infarction These 2 patients made chemical recoveries from coma, but succumbed to the complication

TABLE 4

CAUSES OF DEATH IN 29 FATAL CASES OF COMA IN THE HOSPITAL

Cause	Number
Sepsis and metastatic infection	8
Uncomplicated coma	7
Pneumonia	5
Acute pancreatitis	3
Cerebral hemorrhage	2
Hyperthyroidism	1
Coronary thrombosis	1
Syphilis	1
Toxemia from burns	1

Septic infections including 2 cases with carbuncles, and 1 case each with appendiceal abscess, paranephric abscess, meningitis arising in the mastoid, erysipelas, gangrene of the leg, and possible septic abortion, form the largest single group The 3 cases of acute pancreatitis proved at autopsy occurred in Case Nos 3267, 9987, and 10,115 In 2 cases cerebral hemorrhage was a complicating factor in causing death One of these, Case No 4655, age sixty six years, had had a hemiplegia some years prior to the admission in diabetic coma After a day of headache, dizziness, and vomiting at home, she collapsed two hours before being brought to the hospital Despite 1020 units of insulin and supportive treatment she failed to improve and died in less than twelve hours after admission We considered that she had had a second cerebral hemorrhage No autopsy was performed

Case No 5784 was admitted in coma brought on by fasting and an abscessed tooth She made a satisfactory recovery from coma, but on the eighth day she became disoriented Two days later she had tetanoid convulsions with carpopedal spasms The blood CO_2 was found to be 80 volumes per cent and the blood sugar 0 18 per cent, the blood calcium was 9 6 and 9 2 mg per cent on two successive days She became comatose and two days

later began to have frequent generalized convulsions and died Autopsy revealed multiple small cerebral hemorrhages

High mortality rates have been reported by others when infections and delays in the transfer of patients to the hospital occurred Thus Ashton[3] reports 8 deaths in 22 cases whose average age was 34 7 years All deaths were in females There were no autopsies The causes of death were infection in 4 cases (including pulmonary tuberculosis in one), myocardial insufficiency in one, cerebral hemorrhage in one, and uncomplicated coma in 2 cases The mortality was high but these patients had been in coma a long time before being brought for treatment

Dunlop[4] reports a series of 45 cases with mortality of 60 per cent, but many of these patients were moribund on admission to the hospital Bowen and Hekimian[5] report 10 deaths, of which only 3 were uncomplicated, in a series of 81 coma cases Bertram[6] reports 186 coma cases from Hamburg treated between 1925 and 1931 with a total of 62 deaths He distinguished between "prakoma" and "vollkoma" ("voll erloschenes Sensorium") Among 76 cases of "vollkoma" (the blood CO_2 was usually below 20 to 25 volumes per cent) there were 48 deaths or 63 2 per cent

Of the 160 patients who left the hospital after recovery from coma, 18 have since died, two are untraced and 140 are known to be alive on October 1, 1932 Ten of the 18 were males Pulmonary tuberculosis, ending in 1 case in the miliary form, and in 3 accompanied by terminal coma, appears four times as a cause of death Uncomplicated coma occurred three times and once with an infection Gangrene and coronary disease each occurred in 2 cases Case No 3129, age thirty-two years, at death after diabetes of 10 9 years' duration had at autopsy both carcinoma of the pylorus and a bleeding duodenal ulcer Carcinoma of the colon, pneumonia, general septicemia, and pertussis each accounted for one death Case No 4535 died without clear proof of the cause She took insulin every hour without a physician's attendance and succumbed either to coma or hypoglycemia The average duration of diabetes to death in these

18 fatal cases was 6 5 years indicating that coma, even with recovery, is associated with a prognosis for life shorter than the average diabetic.

Etiology —1 *Age Incidence* —Of the total number of comas treated the hospital children represented 89 and of these there was but one death What a contrast to the period prior to the discovery of insulin when all diabetic children died of coma! But despite such a good record for mortality in the hospital, it is sad to relate that two thirds (44) of all our 66 children, who have died since the discovery of insulin, have actually died of coma Of these 44 children 2 died in the hospital—the one mentioned above in this series, and the other, Tommy D , Case No 1305, who died prior to the series in October, 1922, when insulin was little understood and insufficiently available From August 7, 1922, when we began insulin, until October, 1932, there have been 621 diabetics whose disease began in childhood under our care, and therefore the total mortality of these child hood cases has been 10 per cent and if none had died from coma would have been only 3 per cent for the ten year period How many times outside of the hospital coma developed and recovery took place we do not know, but it does seem as if the death rate outside of the hospital was appallingly high Abolish coma, which all concede to be a preventable complication of diabetes, and it is evident that deaths from diabetes at least in child-hood would practically cease. We have other evidence to sup port this Thus we have 100 living children who already have had diabetes ten years, and 6 fatal cases who lived equally as long Subtract from these 6 fatal cases those due to coma and the 6 deaths are reduced to 3

In the series of 42 coma admissions now reported for the first time only one was an offender on two occasions during the series Six of this group, however, had been treated for coma at the Deaconess Hospital at least at one other time in previous series Eleven or 27 per cent were new patients

2 *Dietary Indiscretions* —Breaking diet is the rule, having occurred in 32 of the 42 individuals Nearly half of these were children One patient developed coma as a result of voluntary

weight reduction Her case presents interesting features because the carbon dioxide combining power of the blood plasma was 12 volumes per cent, whereas the blood sugar was 0 13 per cent The urine contained only 0 6 per cent sugar and a trace of diacetic acid Recovery was very rapid

3 *Infections* —In 8 patients, 19 per cent of the present series, coma was caused by an infection and the 2 fatal cases fell into this group The infections were quite severe Three patients had pulmonary tuberculosis, and in all the diagnosis of tuberculosis was made for the first time upon recovery from coma Two had carbuncles (one also tuberculosis) and one a severe laryngitis

4 *Duration of Diabetes* —The untrained diabetic is most apt to get coma This appears proved by the fact that 49 or 22 per cent of all the series of 221 cases developed coma in the first year of the disease, and 53 per cent occurred within the first three years For further discussion, see page 824

5 *Social Status* —A study of the social status of this present series treated in the hospital showed that only 4 were in good circumstances financially Only 1 patient had a private room and he paid neither for this nor for his medical care Twenty-five patients were in moderate circumstances and 12 were poor Lack of funds with which to purchase insulin was said to be the cause of coma in two instances

These significant facts have led us to investigate the causes of death from coma for the last five years in juvenile patients In 1927 there were 2 deaths, both patients of moderate means, in 1928, 4 deaths, 2 patients of moderate means, 2 poor, in 1929, 2 deaths, 1 patient in good circumstances, 1 poor, in 1930, 1 death in a patient of moderate circumstances It is very striking that in 1931 there were 5 deaths, all in patients who were state, city or town charges

The cost of treatment for coma is great to the patient, to the hospital and to the physician The total hospital charge for the 41 coma admissions at the Deaconess (excluding one Case No 9717 because he was treated at the Palmer Memorial Branch) was $2500 59 of which the patients have paid $2066 79

Since these patients were all treated in the wards and thus at below per diem costs the hospital has lost nearly $1000 caring for them The average hospital cost to the coma patient was $60 99 for his 10 7 days' stay Many, of course, were unable to pay anything for medical care

Yet the above summary does not begin to represent the actual picture A study made by Miss Hunt in charge of the chemical laboratory has recently demonstrated that for each coma case the amount of laboratory work averages the equivalent of $27 even at the low rates prevailing at the Deaconess Hospital Although this is a reduction of 13 per cent as compared with a series in 1930, in fairness it must be said that an unusual number of analyses are done because of our interest in the subject The coma patients do not pay this, because a ward patient is charged but $5 for laboratory expenses for two weeks Miss Hunt's computations were based on the schedule of prices for work done for nonhospital patients for which the rates are as follows blood sugar, nonprotein nitrogen, and CO_2 each $1, cholesterol $3, complete analysis of urine $1, partial analysis $0 05 to $0 30

TABLE 5

DIABETIC COMA ACCORDING TO SEASON—221 INSTANCES 1923–1932

Month.	Number	Month.	Number
January	21	July	8
February	13	August	30
March	19	September	21
April	16	October	29
May	12	November	13
June	18	December	21

6 *Season*—The incidence of coma by months is shown in Table 5 If individual months be selected, August and October are preeminent It is difficult to account for the relative absence of coma in July because diets can be broken then as easily as in August In October there is the fall crop of acute upper respiratory infections, but why is the incidence low in November? If three-month periods be examined, it appears that 86 cases occurred in August, September, and October, whereas the next largest group, 55, was found in the months December to

February inclusive Children formed so large a part of this series, in fact, 100 out of 221, that their return to school in September and exposure to infections may be of importance No explanation seems entirely satisfactory

Clinical Features—1 *Mental State*—Total unconsciousness characterized one sixth of the patients on admission to the hospital, another one sixth were nearly unconscious but could be roused The remainder of the group were conscious although usually drowsy with an anxious expression This can hardly account for the low mortality in the present series because the average CO_2 value (11 volumes per cent) was nearly at the lowest for all 5 series Consciousness is not always an indication of a favorable prognosis, because the 2 fatal cases were conscious on admission to the hospital They recovered chemically from acidosis but died from complications

2 *Respiration*—The Kussmaul type of respiration is usually but not invariably present in diabetic coma In the early stages it is normally present, but as weakness of the patient develops, the respiratory excursions grow less Even when the CO_2 is markedly low, it may be absent [7] Wishiski[8] attributes this to asthenia and circulatory failure caused in his opinion by lack of alkalis in the blood and tissues, particularly in the muscles For this particular group of patients he believes alkalies to be indicated

3 *Circulation*—Coma in elderly diabetics necessarily must prove serious, because arteriosclerosis is so prominent These patients cannot readily withstand shocks such as acidosis or the hypoglycemia which occasionally occurs following recovery Violent shifts of the percentages of sugar in the blood must be disturbing particularly to the heart whose action depends so much upon glucose In an analysis of autopsies upon 100 diabetics Nathanson[9] found coronary sclerosis in 41 per cent and in 53 7 per cent of those above the age of fifty years, while in a larger series of nondiabetics the incidence was only 8 per cent Therefore watch the heart and spare it in diabetic coma!

Circulatory collapse occurred in 5 patients in the present series including the 2 fatal cases The most striking instance

was in Case No 11,138, whose blood pressure could be determined neither by auscultation nor by palpation until eight hours after admission, but she made an uneventful recovery The systolic blood pressure of Case No 11,006 was 45 mm Hg on admission and eight hours after active treatment rose to 80 mm Hg Collapse occurred also in 10,970 These 3 patients recovered The 2 fatal cases, Case Nos 6775 and 11,257, both suffered circulatory failure This was to be expected in the former because he had coronary heart disease and in the latter because he had pneumonia

4 *Renal Impairment*—The present series of 42 cases was notable in the lack of patients with significant kidney disease In only 3 cases was the blood nonprotein nitrogen appreciably elevated On the day of admission Case No 10,893 had a nonprotein nitrogen of 50 mg per cent which rose on the second day to 67, and on the third day to 86 mg per cent This slowly fell to 54 mg per cent seven days later, and was not entirely normal until two weeks after admission Examination of the urine seven months later showed no albumin and a normal sediment. Case No 11,257 was practically anuric at the time of admission and died a few hours later, the blood nonprotein nitrogen was 61 mg per cent On the third day in the hospital, Case No 5267 had a nonprotein nitrogen of 64 mg per cent Four days later this had fallen to 49 and eight days later to 26 mg per cent Case No 11,006 had on admission a nonprotein nitrogen of 54 mg per cent Case Nos 8435 and 11,081 had values slightly above normal In Case No 8435 nitrogen retention with possible renal block caused some confusion in treatment On the second day the dosage of insulin was based on urine tests Green Benedict tests occurred when the blood sugar was over 0 30 per cent and the patient lapsed into coma again because the insulin dosage was decreased too rapidly

If uremia develops in the course of diabetic coma, it is usually associated with anuria and the prognosis is most grave Recently Fullerton, Legall, and Davidson[10] reported 4 deaths among 6 cases of diabetic coma in which the blood urea was over 100 mg per cent and only 1 death among 13 cases in which the urea was

below this level Hypertonic glucose solution (25 per cent) was given in such cases and these authors report recovery in 1 patient who had been voiding only about 2 ounces urine daily for four days and in whose blood the urea had risen to 230 mg per cent

5 *Blood Sugar*—A high blood sugar is not necessarily very prejudicial to recovery from coma, but the usual association of nitrogen retention and a high plasma cholesterol indicate the gravity of the condition In these Clinics we have reported 23 recoveries and 7 fatalities when the blood sugar was or exceeded 700 mg per 100 cc Case No 4099, age twenty-one years, with the highest blood sugar during coma of all our patients, namely 1 62 per cent or 1620 mg per 100 cc , recovered in 1927 and is still alive Case No 3353, age fifteen years with a blood sugar of 1 10 per cent, and Case No 6770, age seventy-two years, with a blood sugar of 1 per cent recovered Two patients, Case Nos 6983 with a blood sugar of 1 04 per cent and 7021 with blood sugar of 1 08 per cent, died Haines and Davis[11] add 3 cases with blood sugar exceeding 1000 mg in diabetic coma who have recovered Their ages were respectively thirty, forty-six, and fifty-eight years In their cases insulin was employed intravenously, as well as subcutaneously, alkalis and salt solution were given subcutaneously, by rectum or with the stomach tube Our Case No 4099 received no alkalis and no intravenous insulin at the hospital but had been given alkali before admission

The lowest blood sugar (0 13 per cent) in the present series occurred in Case No 5776 Her coma was unusual, apparently being due to omission of carbohydrate food or an attempt to lose weight

The anorexia and vomiting which precede unconsciousness for several days are almost equivalent to fasting In animals prolonged fasting seems to affect the power of glucose oxidation Possibly a similar effect is brought about by the lack of food in coma Dann and Chambers[12] found almost complete suppression of the ability to oxidize ingested glucose in the presence of hyperglycemia and glycosuria which occurred in dogs fasted for a period of three weeks In 1 case the nonprotein R Q before sugar administration was 0 71 per cent and after glucose

ingestion was only 0 72 On the other hand, determinations of glycogen, glucose, and lactic acid on portions of the liver and muscles before and after ingestion of glucose indicated that no serious derangement in the process of glycogen formation was produced by the fast

6 *Plasma CO_2*—See "Definition of Coma," p 794 also p 816

7 *Cholesterol*—Determinations of plasma cholesterol were made on 14 patients of this group In 3 cases the blood cholesterol values during coma were well within normal range, 124 to 184 mg per 100 cc In the remaining 11 cases high cholesterol values, 232 to 397 mg per 100 cc. were found and in general these tended to decrease as the condition of the patient improved

These findings are comparable to the larger group reported last year [2] One expects high blood cholesterol values to be present when the fat metabolism of the body does not proceed with regularity and completeness However, one does not find that this happens invariably In approximately 20 per cent of the cases the blood cholesterol value has never exceeded normal

8 *Low Plasma Cholesterol and Hypoglycemia*—Bertram[6] suggests that in cases with low plasma cholesterol values, hypoglycemia is easily produced In this connection it must be remembered, however, that the cholesterol of the plasma as well as the blood sugar are affected by a variety of influences operative not only in diabetes but in other conditions In general an increase in the plasma cholesterol in diabetes is indicative of a relatively more severe disturbance of metabolism Hence the finding of a normal or low plasma cholesterol in cases of diabetic coma would suggest that the coma was either essentially mild or of short duration or both In 3 cases of the present series and 2 cases of the next preceding series the cholesterol values were within normal range and in one instance, Case No 9233, barely above the upper limit In Table 6 these 4 cases are shown to have been very mild cases of coma Not only were they conscious in spite of the presence of Kussmaul breathing, but the eyeballs were not soft and treatment produced rapid improve-

ment The plasma CO_2 was not below 10 volumes per cent The mildness of the coma may be judged by the amount of insulin used and the short period of time required to bring about hypoglycemia or a normal blood sugar In 2 cases hypoglycemia occurred in only five hours Furthermore, the average amount of insulin was but 134 units or hardly more than half the average insulin dose for our whole group of coma cases See discussion under Prognosis

TABLE 6

THE ASSOCIATION OF A LOW PLASMA CHOLESTEROL DURING DIABETIC COMA WITH HYPOGLYCEMIA DURING RECOVERY

Case No	Clinical severity	Upon admission.			Insulin units	Number of hours of treatment.	Blood sugar Gm per cent
		Plasma CO_2 vols per cent	Blood sugar Gm per cent	Cholesterol mg per cent			
8405	Conscious Mild	12	0 28	124	100	5	0 06
7311	Conscious, Mild	16	0 45	161	155	24 108	0 10 0 04
8654	Conscious Mild	12	0 30	184	200	5	0 05
9232	Conscious Mild	19	0 48	232	80	12	0 07

If a close correlation between low cholesterol values and the development of insulin reactions exists, one should find it in the children with hypoglycemia It is true that Case No 5330, boy, age fourteen years, during an extraordinarily severe insulin reaction had a cholesterol value of 129 mg Actually however in 331 analyses Priscilla White[13] showed almost no correlation Thus in 14 children with blood sugar less than 0 06 per cent the mean value of the plasma cholesterol was 227 mg In 92 children whose blood sugar values ranged from 0 20 to 0 30 per cent, the mean cholesterol value was 195 mg per 100 cc

The first explanation, therefore, of the association of hypoglycemia with low plasma cholesterol during recovery from diabetic coma is that one is usually dealing in such cases with especially mild coma However, a low plasma cholesterol value must not be accepted as indicating solely a mild type of coma, because it may be a clue to complications of great importance as follows

(*a*) *Pulmonary tuberculosis* in an advanced stage may produce extremely low cholesterol values Case No 2448 had a plasma cholesterol of 150 mg , a blood sugar of 0 51 per cent, and CO_2 of 34 at 4 45 P M He received 40 units of insulin during the night and at 7 A M the next morning the blood sugar was 0 07 per cent and the plasma cholesterol 90 mg Pulmonary tuberculosis was extensive after diabetes of six years' duration

(*b*) *Hyperthyroidism* may be masked especially during diabetic coma and yet be accompanied by low plasma cholesterol values. Case No 11,203 with auricular fibrillation and hyperthyroidism had a plasma cholesterol of 171 mg before his operation

(*c*) *Pernicious anemia* in an advanced stage characteristically produces a low plasma cholesterol Case No 9859 entered the Deaconess Hospital on January 6, 1932, with diabetes and pernicious anemia His red blood count was 900,000 He was almost moribund The plasma cholesterol was 112 mg and the blood sugar was 0 19 per cent Without insulin, but with intensive treatment by means of liver extract, he made an excellent recovery and at discharge the plasma cholesterol was 169 mg per 100 cc.

(*d*) *Severe inanition* may bring about a low plasma cholesterol and also a low blood sugar In such patients even without insulin, hypoglycemia may occur spontaneously especially if the diet is suddenly reduced Under these circumstances it is not necessarily due to or even accompanied by a low plasma cholesterol Case No 2716, a weak and emaciated woman of sixty-four years, had on July 18, 1922, a blood sugar of 0 33 per cent. The plasma was creamy and the blood fat was 3 4 per cent. Two days later the urine still contained a large amount of sugar The following morning a specimen of urine was found sugar free, the blood sugar was 0 03 per cent, the blood fat 1 9 per cent and the plasma creamy! Weakness was extreme, the pulse was of small volume, and death was expected However, carbohydrate was given every hour and about twelve hours later sugar reappeared in the urine and she made a good recovery

(*e*) *Hepatic insufficiency* may cause one type of hypogly-

cemic acidosis This is noted by Maranon[14] who refers to the experiments of Radvin[15] in demonstrating the failure of glycogenesis and of normal glucose utilization in jaundice and certain types of degeneration of the liver parenchyma Maranon states that in certain cases of hepatitis he demonstrated that the injection of insulin produced an increase of acidosis while reducing the sugar of the blood

9 *Glycosuria and Ketonuria*—Glycosuria in coma does not reach extremes which one sees in the new untreated case Only 23 per cent of the present series of 42 cases had glycosuria over 5 per cent

TABLE 7

GLYCOSURIA IN COMA—113 CASES

Glycosuria per cent.	Number of cases
0.1–0 9	4
1 0–1 9	11
2 0–2 9	16
3 0–3 9	28
4 0–4 9	30
5 0–5 9	14
6 0–6 9	9
7 0–7 9	1

Absence of diacetic acid occasionally occurs in coma, especially when failing renal function results in a retention of ketone bodies in the blood stream Among the 179 cases previously reported are 5 patients who did not have ketonuria at the time of entrance One had been given 310 units of insulin prior to admission, one was unexplained, 2 were moribund (one with septicemia, and one with acute pancreatitis) and the fifth had a paranephric abscess Richardson's[16] patient was comatose without diacetic acid in the urine The plasma CO_2 combining power was 7 volumes per cent and the eyeballs were soft The urea nitrogen of the blood was 35 mg per 100 cc In this case it was felt that possibly all the ketone bodies were in the form of β-oxybutyric acid rather than as acetone or diacetic acid Lemann[17] has described cases presenting glycosuria without ketonuria in association with cerebral hemorrhage without preceding history of diabetes

In a review of present-day ideas regarding acidosis in diabetes, Rudesill[18] stresses the mineral metabolism Loss of chloride through vomiting and through excretion in the urine as ammonium chloride are important factors in dehydration Peters and Van Slyke[19] state that in acidosis the loss of chloride from the tissues is far greater in amount than the loss of chloride from the blood serum

Lichtwitz[20] also states that ketonuria of higher degree develops through an impoverishment of the body with respect to alkali because the ketone bodies are eliminated for the most part as salts through the kidneys This loss of base is lessened by the fact that the kidneys excrete a urine of highest possible acidity and also the kidneys form ammonia from urea H^+ and NH_4^+ therefore act as kations for the anions of the ketone bodies Ketonuria is not of the same significance as acidosis It may occur in alkaline states such as over treatment with insulin The presence of acidosis may be measured by the excretion of ammonia in the urine, but more satisfactorily by the CO_2 combining power of the plasma

10 *Cases with Complications—Pregnancy*—The hazards of coma during pregnancy in the young diabetic are illustrated in Case No 2776 whose coma was precipitated either by the death of the fetus or by the onset of labor This patient was nineteen years of age and had had diabetes 52 per cent of her life Her diabetes had never been under control In the sixth month of pregnancy she developed pyelitis and acidosis, because of which she entered the hospital Following this she became a very cooperative patient. She returned to the hospital for periodic examinations and entered for delivery on September 30th Her diet was carbohydrate, 160 Gm , protein, 65 Gm , fat, 90 Gm , weight 138 pounds She had slight edema, otherwise her physical examination was negative Her diet was relatively rather low, but was kept at this level with the hope of controlling the size of the baby She remained sugar free until the third day before delivery when her sugar reappeared and gradually increased The urine also had a trace of diacetic acid and subsequently her insulin dosage was increased She stated that she

felt fetal motion During the night of October 13th labor started and she was transferred to another hospital for delivery At this time she was excited, flushed, and slightly hyperpneic Membranes were ruptured at 9 A M She was given sodium amytal anesthesia At 1 P M she was barely responsive, and had deep Kussmaul breathing The carbon dioxide combining power of the blood was 6 volumes per cent and the sugar 0 33 per cent During the next twenty-four hours she was given 510 units of insulin, gastric lavage was done three times, and she received 750 cc of 10 per cent glucose intravenously During the course of treatment she would make temporary improvement and then as labor became more active she would slip back into coma both clinically and chemically At 10 30 P M she was delivered of a macerated fetus weighing 9 pounds At autopsy it was believed that the fetus had been dead at least forty-eight hours Was her coma precipitated by the loss of insulin which resulted from fetal death (?!), by the changes in metabolism which occurred in labor or because of the sudden loss of 7 pounds of weight in five days? After delivery she made rapid improvement

Although acidosis may cause death of fetus in utero this is not an invariable rule Case No 7565 was treated for coma in the sixth month of pregnancy and delivered by cesarean section at eight and a half months of a healthy baby Case No 3040 also had mild acidosis during pregnancy, and was delivered of a baby who is healthy now, but who did develop unexplained edema after birth Case No 6406 was delivered of a macerated fetus twenty-three days after she no longer felt fetal motion At no time after death of the fetus did her sugar increase or did she have signs of impending acidosis

These experiences lead us to conclude that in the future we will advise delivery by cesarean section in any primipara with diabetes unless of obviously mild severity

Appendicitis—Acute appendicitis and severe acidosis developing later into coma occurred in Case No 7311, illustrating again the importance of differential diagnosis of coma and an acute surgical abdomen

Case No 7580 had onset of coma following tonsillectomy and omission of insulin

Case Nos 8435, 5932, and 11,006 had pulmonary tuberculosis In none of these was the diagnosis of tuberculosis made prior to coma These patients made slow recovery and one slipped back into coma twenty four hours after recovery from the first coma

Differential Diagnosis—We regret that space forbids detailed discussion of this most important subject In nearly all our publications certain aspects of this problem have been reviewed In earlier clinics[2] in this series as well as in the most recent monograph from our group[13] unconsciousness due to insulin hypoglycemia uremia, meningitis, etc have been repeatedly mentioned In 1931, 2 deaths occurred in our children outside of the hospital and not under our immediate care which may be directly attributed to hypoglycemia wrongly treated as if it were diabetic coma This has emphasized to us the importance of stressing simple measures for the differential diagnosis of these two conditions

In distinguishing between hypoglycemia and coma, Sehestedt [1] brings up again the question of the plantar reflex He states that in insulin shock, particularly in cases of actual unconsciousness, the Babinski sign is frequently positive on one or both sides He has never found it positive in diabetic coma nor seen a statement to that effect We have not observed it in either condition, perhaps because our attention has not been sufficiently directed toward it

Prognosis—One hundred and four or 47 per cent of the 221 coma cases were under the age of twenty years, but only 3 or 10 per cent of the 29 coma deaths were in patients in the first two decades In fact, there were no deaths under ten years of age and in the second decade the mortality was only 3 per cent in contrast to 13 1 per cent mortality for the entire series In the fifth decade the mortality rose to 23 per cent, in the sixth to 30 per cent, and in the seventh to 27 per cent. There were but 3 cases in the eighth decade with but one death

One is tempted to ask if early detection and better blood ves

sels are the only reasons for the immunity of children to death by coma when they receive treatment, since we must not forget that after all more children die of coma than of any other complication, in fact even since the discovery of insulin fully two thirds of the deaths in children are due to it Allowing that the coma was detected earlier in children, was it of less severity? The facts are as follows

TABLE 8

MORTALITY OF DIABETIC COMA RELATED TO AGE AND SEVERITY AS MEASURED BY THE CO_2

Age at coma by decades	Total cases	Average CO_2 vols per cent	Per cent fatal cases
First*	10	12	0
Second	94	13	3
Third	26	13	8
Fourth	23	13	9
Fifth	26	11	23
Sixth	27	12	30
Seventh	11	14	27
Eighth	3	5	33†

* One case not included because CO_2 not done
† One patient died of pneumonia

Table 8 indicates that the severity of coma as measured by the CO_2 was practically the same in each decade except the eighth

It is self-evident that the longer a patient is unconscious before the institution of treatment, the worse the prognosis It is seldom that patients in this community are really unconscious more than three to five hours before admission to a hospital Case No 10,970 had been unconscious eleven hours before admission, but made a good recovery Case No 3240 was said to have been unconscious for a day and a half prior to admission, yet she responded feebly to questions three hours later While in coma she was brought by automobile 100 miles to the hospital Her death within four hours of admission in 1923 we felt due more to exhaustion from the long delay in treatment and to a dilated stomach Umber[22] feels that after eight hours, the prognosis is bad Bertram[23] expresses about the

same view, although he has seen recoveries after ten to twelve hours of unconsciousness

Prognostic signs are many and none are infallible All recognize the relatively serious import of a low blood pressure or more particularly a blood pressure that falls steadily despite treatment Likewise cardiac irregularities, myocardial and renal disease, "renal block" and a very high or rising blood nonprotein nitrogen indicate a poorer, though by no means hopeless, out look Bertram regards blood sugar values of 0 7 to 0 8 per cent or more and CO_2 values of less than 10 volumes per cent as bad prognostic signs although not uniformly so In our total series we have had recoveries with blood sugar values as high as 1 6 per cent and with CO_2 values as low as 2 volumes per cent Bertram regards a value of over 70 mg per cent for total acetone in blood as unfavorable, marked lowering of the freezing point of the blood serum is likewise a bad sign He finds a lymphopenia in some cases (in one instance not one lympho cyte in 200 white corpuscles) and in these the outlook is doubtful He states that patients with an initial low or normal serum cholesterol tend easily to hypoglycemic shock For discussion of this point, see page 809

In general, plasma CO_2 values below 10 are so frequently associated with severe complications, especially in the aged, that they connote a serious prognosis Yet Case No 3750, age thirty four years, reported in a previous series walked into the hospital when the CO_2 combining power of her blood was 2 volumes per cent

The future course of the disease was little affected by the coma so far as the tolerance for carbohydrate, requirement for insulin, the blood sugar and glycosuria are concerned These patients took on the average 7 units of insulin more after the attack of coma than before Among our old patients the aver age blood sugar was 0 18 per cent before coma and 0 16 per cent on the latest visit after coma. The average degree of glycosuria was the same, 1.5 per cent, and the average number of grams of carbohydrate in the diets was essentially the same before and after coma

Repeated Offenders—In the entire group of 221 instances of coma, 58 were due to 25 patients who had coma two times or more under our observation in the hospital (Here one should repeat that by "coma" is meant acidosis so marked that the plasma CO_2 is 20 volumes per cent or lower) Case No 3877 had coma 6 times, Case No 6287, 4 times, Case Nos 4232 and 3682, 3 times, and 21 other cases, 2 times each Of these 25 patients 22 are still living Various complications arose in this series of 25 patients The outstanding complication has been pulmonary tuberculosis Case Nos 4232 and 6287 have developed active pulmonary tuberculosis, while Case Nos 7251 and 6649 show changes in the roentgenogram considered so suggestive of early pulmonary tuberculosis by Dr L B Morrison as to be classified as "suspicious" The development of this disease would appear more striking if certain cases were included in whom the later attacks of acidosis were recognized before the plasma CO_2 fell to our critical level of 20 volumes per cent Thus Case Nos 2687 and 2448 are not included for this reason, yet both died of pulmonary tuberculosis Hirsch-Kauffmann[21] also cites a sixteen-year-old child with onset of diabetes in 1925 who had coma twice She took 120 units of insulin in three doses In May, 1928, she developed an apparently influenzal infection and *x*-ray showed an active tuberculosis of right upper lung, again illustrating the danger of tuberculosis in children who have had coma

Not only acidosis but the long duration of diabetes in this group brings other complications Sclerosis of retinal arteries was noted in 5 cases with duration of ten years in 2 and of 9, 8, and five years in the other 3 Vascular changes in kidneys or legs occurred in 3 and septic infections in 5 Case No 3129, age thirty-one years at death, is notable because carcinoma of the pyloric portion of the stomach in addition to a duodenal ulcer was found at autopsy

The pathogenesis and prognosis of coma are exhaustively reviewed by Bertram[23] with a careful analysis of 60 cases from the first medical service of the Barmbeck General Hospital, Hamburg His bibliography includes 218 references to authors

He gives a valuable summary of 1007 cases of coma reported by 25 authors since the use of insulin and shows the average mortality to be 29 1 per cent He follows Schmidt and divides coma cases into the hypertonic and asthenic types The hyper tonic or sthenic group are older, usually have high blood pressure, have a tendency to develop gangrene or arthritis The asthenic type are usually under thirty years of age with normal or low blood pressure and develop ketonuria easily This division seems arbitrary A more natural classification is by age

Treatment.—We have seen no reason to change our methods materially since our clinic of a year ago Again we urge the importance of early recognition of the condition and prompt institution of treatment

A patient in coma is usually a patient in shock His extrem ities are cold, his body temperature and the blood pressure are often low the pulse weak and rapid, the muscles lack tone, and the reflexes may be absent These are the facts to bear in mind and they point the way for treatment For these reasons when the telephone warns that a coma patient is on the way to the hospital, blankets, heaters, insulin, salt solution, stomach and rectal tubes are assembled and provision made for immediate presence of sufficient nurses, the doctor and laboratory tech nician One individual could attend to all these features of treatment, but precious time is saved by drafting the services of many workers Time counts as everyone agrees Why not save it for the patient? Night is day just as it is in obstetrics

The treatment other than the supplying of warmth, may be summarized as follows

1 *Insulin*.—We reaffirm the advantage of frequent divided doses of insulin in preference to one large initial dose as advised by Müller [25] On admission 20 to 50 units are given upon the clinical evidence and tests of urine before the result of the blood tests is known The initial dose, whatever that may be, is usually repeated half an hour later and so on until clinical and chemical evidence show improvement The chief concern is to give sufficient insulin, as emphasized by Freise and Jahr [6] Usually we feel that an unconscious case requires 200 units in

the first two hours Then urine tests for sugar are ordered every one or two hours and insulin prescribed varying with the degree of reduction of Benedict's solution, as 15 units for a red test, 10 for a yellow, or 5 for a green reaction If necessary the urine is obtained by catheterization, with care for the protection of the bladder We employ micro tests of capillary blood for sugar whenever possible so as to conserve the veins

2 *Fluids*—The coma patient is always dehydrated He must have liquid It is seldom that one can postpone the administration of 1000 to 1500 cc of normal salt solution subcutaneously (by gravity) beyond the first hour and occasionally, in addition, 500 to 750 cc administered intravenously are required All solutions must be given slowly, must be slightly above body temperature, and one should not forget that the child's needs for fluids, due to his size, are barely half that of an adult twice the size Following the cleansing enema rectal fluids may be given, but absorption is uncertain With freedom from vomiting, fluids by mouth are allowable, but despite the wishes of the patient, these should be restricted to from 60 to 100 cc an hour Otherwise the stomach may become dilated, vomiting result, and death occur even if other therapy has been adequate

3 Gastric lavage is of great value and it is rarely omitted Time and time again we have obtained large quantities of fluid, food remains and old blood by careful lavage of the stomach Dilatation of the stomach and vomiting are thereby relieved and within a short time fluids by mouth can be resumed cautiously Without gastric lavage not only does the dilated stomach cause pain and abdominal distress, but the heart action is embarrassed, and vomiting becomes a serious feature

4 A cleansing enema is routinely given

5 Circulatory stimulants appear indicated particularly in adults, but the action of no drug is sufficiently specific as to be considered satisfactory We have never used camphor and recently have employed less caffeine Ephedrine has been given either subcutaneously in doses of 0 5 to 1 cc (25–50 mg) or intravenously in doses up to 1 cc Adrenalin is also used for extreme collapse The size of the dose and time interval must

be chosen to meet the situation at hand In the present series of 42 cases, only 4 were given stimulants, in these 4 ephedrine was employed and in 2 of them also adrenalin and caffeine in the attempt to raise the blood pressure Müller[5] advises the use of strophanthin, cardiazol, camphor, and caffeine Bertram uses strophanthin, camphor, caffeine, and strychnine

In this clinic glucose, orange juice, ginger ale or other forms of carbohydrate are not given by mouth during the first few hours of the treatment of coma unless the percentage of blood sugar falls to a reasonable level Intravenous injections of glucose solution have only been used in extreme collapse when fluids given under the skin were not properly absorbed Our idea has been that with such an excess of unused sugar in the blood stream it is beside the point to add more Himsworth[2] believes this point of view wrong and insists that the diabetic in acidosis needs "glucose covered by insulin and not insulin covered by glucose" He and other clinicians, who give glucose freely from the start, report good success but it is unfortunate that in many of these articles full data as to the number of cases, age of the patients, the degree of acidosis (as measured by the CO_2 combining power of the plasma), are unpublished One cannot compare results of treatment of diabetic coma without facts It is only fair to state, however, that we have usually given some carbohydrate by mouth or vein within at least six to eight hours from the time of institution of treatment and that the usual patient receives 50 to 100 Gm of carbohydrate within his first twenty four hours in the hospital We give carbohydrate for food rather than for coma

Alkalis are never given For justification of their avoidance we point as before to our own statistics of mortality

Two incidents may occur in the course of treatment of diabetic coma which merit especial comment

1 *Hypoglycemia*—A fall in blood sugar to 0 07 per cent without symptoms within ten to twelve hours is often favorable for early recovery Hypoglycemia with collapse is rare, if the patient and laboratory tests are closely watched Is it because our cases of coma are more severe than those of other authors

that we seldom have severe hypoglycemia during the course of treatment? Bertram[23] states that patients with a normal or low initial value for blood cholesterol are especially prone to hypoglycemia As a matter of fact, in our present series 4 patients had a normal cholesterol, in 2 cases, the blood sugar fell to 0 05 and 0 06 per cent within five hours

2 The return to a condition of coma after apparent recovery Such a complication is rare in a well-regulated hospital, but it does occur Without adequate laboratory facilities it is sure to be met with more frequently After having treated and reported over 200 cases of coma, originally proved and later controlled by chemical tests, we unanimously agree and emphatically assert that it is not possible to be sure of the diagnosis, or progress of treatment of diabetic coma in all cases without assistance of the laboratory Why take a chance to steer without a compass when such is available? Muller[20] writes that "it is extremely difficult, indeed we might say impossible, rightly to treat a coma patient without a knowledge of the blood sugar and the alkali reserve At any rate the outlook for the patient falls quite extraordinarily without a knowledge of these facts For this reason each patient with beginning or outspoken coma belongs in a clinic"

Laboratories are veritable Islands of Safety for diabetics and we should promote their existence and see to it that they are within the radius of twenty miles of every patient Laboratories should be utilized and we should remember that the cost per test decreases with the number of tests performed Therefore, stimulate the output and decrease the cost If a laboratory charges $10, $5 or even $3 for each blood sugar test it lessens the effectiveness of that laboratory in its combat with diabetic coma

It has long been known that the surgical diabetic is the serious diabetic and the diabetic who dies, but it is not sufficiently understood that the poor diabetic is in a similarly serious situation and that he it is who develops coma and will die if we do not protect him Gottschalk[1] concludes the fate of the patient depends upon (1) his intelligence and perseverance, (2)

his social condition and, finally, (3) on the competency of the doctor who treats him Reinwein's[28] study of the outcome of diabetics treated in Würzburg at Grafe s clinic clearly indicated the influence of poverty In 1931 the only diabetic children we lost were those dependent upon aid from town, city or state

Diabetic coma in a diabetic child or adult can be avoided when in a hospital, but it is almost too much to expect that it will never appear in the home It is a characteristic of the disease in children At least 10 per cent, and probably 20 per cent or more, of all our children have had coma at least once Often the diagnosis of diabetes is first made in coma In fact, the diabetic child is seldom forty-eight hours removed from the possibility of coma and it will appear if gross errors are made in diet or insulin But it can be avoided provided the child and the relatives are properly taught It is the neglected child who develops it If diet is followed and urine kept sugar free, coma stays away, but with carelessness about diet or insulin the development of an infection, or, in fact, most any complication, coma is just around the corner At the slightest sign of any indisposition, therefore, we teach the patient (and we repeat the rules again in this clinic) to (1) call the doctor, (2) go to bed, (3) drink a cupful of hot liquid every hour, (4) take an enema, (5) keep warm, and (6) get a nurse or someone to wait upon him These rules must be learned by heart by the patients and their relatives if our diabetic children, or adults for that matter, are not to succumb to this needless complication Furthermore, it behooves every doctor who has a diabetic patient under his care, whether child or adult, to be alert, first, to prevent coma, second, to detect it quickly, and, third, to be prepared either to treat it or to send the case to the hospital

As certainly as one thinks of cancer if a woman has a lump in her breast or an old man has blood in his urine, so think of coma if a diabetic is reported to have nausea, indigestion, indisposition, particularly in the course of an infection or when having difficulties with diet or insulin, and be prepared for action

In Table 9 we have tried to evaluate the results of our efforts to educate our patients It would appear that the untrained

diabetic, the diabetic with disease of short duration, is the one who is most apt to contract coma

TABLE 9

DURATION OF DIABETES PRIOR TO COMA

Duration diabetes, years	Cases of coma	Duration diabetes years	Cases of coma
0–1	49	6– 7	17
1–2	34	7– 8	10
2–3	34	8– 9	7
3–4	26	9–10	3
4–5	19	10–15	5
5–6	16	15–20	1

Of the 221 cases of coma treated from 1923 to 1932, 49, or 22 per cent, occurred in patients who had had the disease less than a year and 53 per cent of all the cases occurred in patients who had had the disease less than three years

This is shown also by comparing the cases which were seen first during coma as opposed to those "old cases" who developed coma subsequent to their first visit to the clinic From 1925 on, regularly about one third of the cases of coma were in patients seen for the first time In a twenty-three month period 1925 to 1927 apparently about 1 in 200 of our old patients developed coma and came under our personal care and during this last year the proportion was about 1 to 150 to 175

Condition at Discharge —In Table 10 are shown the dis-

TABLE 10

CONDITION OF LAST 24 PATIENTS FOLLOWING DIABETIC COMA IN 1932
DIET, INSULIN, AND WEIGHT AT DISCHARGE

Age years	Number cases	Diet in grams.				Weight Kg	Cals per kg	Insulin units	Days in hospital
		Carb	Prot	Fat	Cals				
8–10	2	142	69	72	1492	23 8	63	25	9
10–15	3	127	74	80	1524	32 5	48	41	7
15–30	12	137	69	84	1580	50 9	33	44	14
30–50	5	126	63	91	1575	49 8	32	37	17
50–60	2	127	67	93	1613	60 1	28	28	16
Averages 1932	24 cases	133	68	83	1551	46 9	37	39	13
Averages 1931	19 cases	141						41	15

charge diets and insulin of the last 24 patients in the present coma series and including all those treated in 1932 As will be seen the amount of carbohydrate given is practically the same as in 1931 The calories per kilogram of body weight vary inversely with age from 63 in childhood to 28 during the sixth decade Usually increases in diet are accomplished after discharge from the hospital when the patient is able to resume full activity

Summary —1 The records of 221 cases of coma occurring in 189 diabetics with 29 deaths are analyzed Since discharge from the hospital during the last nine years 18 more cases have died Two cases are untraced, 140 cases have been traced to October 1, 1932 The mortality of the present series of 42 cases is 5 per cent, and of the entire series of 221 cases is 13 1 per cent

2 Sixty three per cent of the cases were females

3 In August, September, and October occurred 86 of the 221 cases

4 Insulin dosage during the first twenty four hours was 201 units as compared with 252 units in the previous 74 cases Three cases received 510 to 520 units and all recovered

5 The mortality in coma increased from 0 (11 cases) in the first decade to 3 per cent in the second decade, 8 and 9 per cent in the third and fourth, and reached a maximum of 33 per cent for 3 cases in the eighth decade

6 The chief cause of death in the hospital for 29 cases was sepsis and metastatic infection, and the most frequent cause of death after discharge from the hospital was pulmonary tuberculosis

7 Twenty two per cent of the cases occurred in the first year of diabetes

8 Eighty-eight of 89 children with onset of diabetes before the fifteenth year recovered from coma

9 In 14 cases the plasma cholesterol was studied and found within normal limits in 3 cases A low cholesterol value in coma is highly important, suggesting first a mild type of coma in which insulin must be used conservatively to avoid hypoglycemia, and second, complications such as pulmonary tuber-

culosis, hyperthyroidism, severe pernicious anemia, or severe inanition

10 Complications with pregnancy and appendicitis are reported

11 At discharge from the hospital in 1932, the diets contained an average of carbohydrate 133 Gm, protein 68 Gm, and fat 83 Gm

12 We feel that there should be far greater endeavor to prevent diabetic coma in the community We should more actively follow up all our diabetic cases after discharge and see to it that they keep in contact with their family physicians The usefulness of this has been emphasized and demonstrated by Gottschalk[1] of Stettin

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CLINIC OF DR FREDERICK T LORD

FROM THE MEDICAL SERVICES OF THE MASSACHUSETTS GENERAL HOSPITAL

THE ETIOLOGY, PATHOGENESIS, AND DIAGNOSIS OF ACTINOMYCOSIS

I SHOULD like to discuss certain aspects of a rare and interesting disease, actinomycosis, in connection with the presentation of a case

Terminology—As there is much confusion with respect to terminology, let me define the disease as an infection, characterized by the usual presence of lesions composed of abundant granulation or connective tissue surrounding multiple areas of abscess formation and by the presence within the abscesses of the specific infecting agent in compact colonies composed of branching, gram staining, filamentous, anaerobic organisms with radially disposed, club-bearing filaments

The nomenclature for branching, filamentous organisms is a troublesome matter It is on the whole fair to say, however, that most investigators actually working in this field have long regarded the disease I have defined above as actinomycosis and that this designation has the merit of prevailing usage among such investigators There is, however, a tendency to include other branching, filamentous organisms forming colonies with radiating filaments and clubbed terminal portions under the term "actinomyces" and to use the terms "actinomyces," "streptothrix," and certain others as synonyms So far as the streptothrix is concerned, this term has in general been applied to aerobic organisms which though closely related are widely different from actinomyces in biologic peculiarities and there are important differences in the mode of origin of the resulting

disease and the clinical picture To use actinomyces and streptothrix as synonymous terms obscures the hard-won distinctions between them and tends to undo much which has already been accomplished

Etiology—Let me remind you that there are two widely different points of view regarding the etiology of the disease There is on the one hand the view based on Bostrom's[1] observations that it is due to aerobic organisms which abound in the outside world, especially in vegetable material, and gain entrance to the body from without and there is on the other hand, the view based on the investigations of Wolff and Israel[2] that anaerobic organisms, growing only at body temperature, are concerned A difference of opinion regarding this matter is, I think, due to the fact that the type of disease and the type of organisms have not always been closely correlated and, in addition, that owing to the difficulty of obtaining pure cultures of actinomyces bovis, many writers are personally unfamiliar with the biologic characters of the organism

Bostrom isolated an aerobic, branching, filamentous organism from actinomycosis of the jaw in cattle But it is important to note that about 700 cultures were made from 11 cases and that from 7 of these he obtained only 12 single, separate growths or colonies It is significant also that the experimental inoculation of animals with these pure cultures failed to produce any characteristic pathologic lesions A wide distribution in nature of such nonpathogenic aerobic organisms as he described is well known and makes it probable that a positive finding in so small a proportion of the cultures is to be ascribed to contamination of the cultures or the occurrence of secondary invaders in the animal lesions Many observations on the recovery of organisms more or less similar to those found by Bostrom from human and animal lesions have since been reported In the bacteriological investigation of ten infections of a nonactinomycotic nature, Naeslund[3] obtained, in four, pure cultures of

[1] Beitr z path Anat. u z allg Path , Jena, *1890*, ix, *1*
[2] Virchow's Arch f path Anat , 1891, 126, 11
[3] Acta Path et Microbiologica Scandinavica, Suppl VI, 1931

aerobic organisms similar to those described by Boström and nonpathogenic for animals

The first extensive investigation of the biology of the micro organism of actinomycosis was published in 1891 by Wolff and Israel [1] From 2 cases of human actinomycosis they cultivated a branching, filamentous, gram-staining organism which grew best under anaerobic conditions at incubator temperature and not at all at a room temperature of 16 to 20 degrees

In the next few years a number of observers reported the isolation in pure culture from human or bovine actinomycosis of organisms similar or apparently identical in character to those described by Wolff and Israel The most important confirmation of their findings, however, was made in 1905 by Wright.[2]

Without going further into the matter from these and subsequent observations, the etiologic relation of organisms of the Wolff Israel type to actinomycosis must, I think, be regarded as established There are still, however, unsolved problems in this connection, such as the relation of other branching, filamentous organisms to those of the Wolff-Israel type and the importance, if any, of the synergistic action of other organisms in causing the disease Let us now consider the problem of the origin of the disease

Pathogenesis —In 1904, I noted in the sputum from patients with various types of nonactinomycotic respiratory infection the occasional presence of organisms with the morphology and staining reaction of actinomyces, appearing as isolated filaments or aggregations of filaments forming a small granule without clubs and much mixed with other bacteria The attempt to isolate the organism in pure culture at that time failed and the results of subcutaneous inoculations of animals with contaminated bouillon cultures were negative

My attention was again directed to the problem of the origin of the disease, a few years later, by the history in several patients with actinomycosis of much trouble with the teeth

[1] Virchow s Arch f path Anat 1891 126 11

[2] Publications of the Massachusetts General Hospital vol. i No 1 May 1905

preceding the onset of the affection and by a review of the literature My previous finding of organisms resembling actinomyces in the sputum, the failure of actinomyces to grow at other than body temperature and the lack of evidence that actinomycosis is a contagious disease suggested that infection arises from within rather than from without the individual The prevailing location of the disease in the cervicofacial region naturally suggested the mouth as a source and led me to investigate this region

For the purpose of the investigation, patients without actinomycosis were selected Organisms with the morphology and staining reaction of actinomyces were constantly demonstrable in smears and serial sections of material from the contents of carious teeth and in serial sections of yellowish, hard or soft material from the tonsillar crypts The intraperitoneal inoculation of guinea-pigs with this material and with the scrapings from sound teeth gave rise to omental tumors histologically identical with actinomycotic tissue and containing typical club-bearing actinomyces granules, in 60 per cent of the inoculations [1]

These findings furnished evidence in favor of the buccal cavity as a normal habitat of actinomyces bovis and the source of infection To prove the identity with actinomyces bovis of the organisms found in the normal mouth and in the experimental lesions in animals, however, it would be necessary to work with pure cultures on account of the possibility of the existence of other organisms similar in morphology and staining reaction and capable of causing lesions identical with those of actinomycosis and with typical club-bearing colonies Cultures from the original material and from the animal lesions were made in bouillon and sugar agar Branching, filamentous organisms resembling actinomyces were readily demonstrable in bouillon tubes and colonies with radiating, branching filaments developed in the suspension sugar agar tubes, but I was unable to obtain pure cultures on account of the abundance of contaminating organisms

Further evidence in favor of the origin of actinomycosis from organisms harbored in the mouth by normal persons has been

[1] Lord Jour Amer Med Assoc., October 8, 1910

obtained by Naeslund[1] who in confirmation of my findings produced typical actinomycotic lesions in animals inoculated with material from the contents of carious teeth saliva, and dental scum He also investigated the bacterial flora of the mouth for actinomyces The material was obtained from the mouth of healthy persons and from extracted and chiefly carious teeth Surface cultures were made in Petri dishes containing large amounts of sterilized saliva and in a number of cases small amounts of glucose and ascitic fluid Anaerobic conditions for cultivation were secured by means of McIntosh and Fildes apparatus with electric heating of palladinized asbestos He succeeded by these means in obtaining from the mouth cavity of normal persons pure cultures of anaerobic organisms morphologically, culturally, and serologically similar to actinomycetes of the Wolff Israel type and capable of giving rise in animals to typical actinomycotic lesions with club-bearing granules

During the summer of 1932, I succeeded by the use of the McIntosh and Fildes method of anaerobic cultivation in the isolation in pure culture of actinomyces from the normal mouth of 2 of about 70 patients without actinomycosis In both cases the inoculated material was obtained from scrapings from the teeth The organisms may be briefly described as follows They grow at incubator temperature under completely anaerobic conditions and also under access of air Young colonies show radiating, branched and unbranched filaments No aerial hyphae or spores are formed. Smears show gram staining, nonacid fast, branched and unbranched, long and short filaments The morphology is variable Short, bent rods, diphtheria like forms, filaments with staining points and areas and filaments with club-shaped terminal portions are at times observed Plain or dextrose bouillon cultures with access of air show growth as a soft, friable, amorphous sediment without odor, clouding of the medium or surface colonies Suspension dextrose agar cultures in the presence of oxygen show small, round, grayish-white colonies throughout the medium On slanted media under aerobic conditions growth occurs in the form of grayish white,

[1] Acta Path et Microbiologica Scand 1925 2 S 110 Ibid 1931 S VI

opaque, discrete or confluent, nodular, soft, moist, shiny colonies, somewhat adherent to the surface No proteolysis is observed No growth is observed in milk or pleural fluid

There are certain practical matters with respect to the diagnosis of the disease and these may well be considered in connection with an individual case

Case History of Patient with Multiple Inflammatory and Suppurative Lesions —On April 27, 1899, B C , female, age twenty-eight years, single, worker in a bake shop entered the Massachusetts General Hospital, with a history of pain for six months in the right lower part of the chest After the pain had lasted about a week she noted a swelling in the right back below the angle of the scapula She had lost weight There was no cough or dyspnea Examination at entrance showed a red, tender fluctuant area with indurated margins in the right back below the angle of the scapula and between the spine and the posterior axillary line Incision and drainage of the affected region on the second day after entrance yielded thick, yellowish-brown fluid and necrotic tissue. Her progress was, nevertheless, unfavorable and within the course of two months three sinuses had formed and the inflammatory process was found to extend into the thorax On June 29th on resection of a part of the tenth rib the underlying tissue was found to be infiltrated In the following three months she continued to do badly On July 27th she had two convulsions On August 12th she was noted to have an abscess on the inner aspect of the right foot and on the 16th another in the right thigh Both were incised On the 27th there was an abscess in the abdominal wall just to the right and above the navel Throughout she had an irregular fever She died on September 1, 1899

Discussion of the Diagnosis from the Clinical Aspect —The condition was apparently at first an inflammatory and suppurative process confined to the thoracic region with gradual extension into neighboring tissues and later the development of multiple, metastatic abscesses The complex is to some extent consistent with tuberculosis, glanders, and systemic blastomycosis Though the thoracic process might be tuberculous, the dissemination of tubercle bacilli does not ordinarily give rise to multiple, large, local, suppurative areas Glanders is unlikely from the patient's occupation and the absence of nasal symptoms, but cannot be excluded without bacteriological examination of the pus With blastomycosis skin lesions may be expected, but microscopical examination of pus or tissue should be made to establish or exclude it

The clinical aspects are especially suggestive of actinomycosis, or of streptothricosis As these terms may be somewhat confusing, I should like to use them with the explanation that by the term "actinomycosis" I have in mind an infection with an anaerobic organism found in the suppurative lesions in the form of compact colonies composed of branching gram-staining, filamentous organisms with radially disposed, club-bearing filaments, and by the term "streptothricosis" an infection with aerobic organisms with a tendency to form loose rather than compact colonies composed of gram staining filaments without true clubs

Though these two organisms give rise to disturbances with much in common, there are important differences in the clinical picture The primary site of actinomycosis is in the cervicofacial region in about half of the cases Involvement of the abdominal region is next in frequency and embraces about 30 per cent of the cases, while the thoracic form of which the case under consideration is an example comprises about 20 per cent The disease arises from organisms normally harbored in the mouth, hence the predominant involvement of the neighboring regions and invasion of the abdomen by swallowed organisms The thoracic form may be regarded as arising from the aspiration of organisms from the buccal cavity or by extension from the cervicofacial region or the esophagus Streptothricosis is rarely primary in the cervicofacial or abdominal regions It is usually primary in the lung and may be assumed to arise in consequence of organisms which gain entrance to the body through the inspired air

The lesions in both actinomycosis and streptothricosis are inflammatory and suppurative with the production of a varying amount of granulation and connective tissue surrounding multiple areas of abscess formation The formation of communicating channels and discharging sinuses is common to both Granulation and connective tissue is a prominent feature of actinomycosis and abscess formation a prominent lesion in streptothricosis

In both actinomycosis and streptothricosis extension takes

place locally from the primary focus by invasion of contiguous tissue General distribution is by way of the blood stream and not the lymphatic system Metastases are rare with actinomycosis They are much more common with streptothricosis in which there is a special tendency to cerebral involvement

The outlook differs in the two groups of infection Actinomycosis usually runs a slow course with a tendency to recovery in the cervicofacial and to a less extent in the abdominal type, but with little chance of a favorable outcome in the pulmonary form On the other hand, streptothricosis usually runs a rapidly fatal course

Such differences in the clinical aspects are of principal diagnostic value in the cervicofacial type, which is almost always actinomycotic in nature They have no more than a suggestive value in other types and the diagnosis cannot be made from the clinical aspects alone in individual cases Thus in the case under discussion the apparent lack of pulmonary involvement is against streptothricosis and in favor of actinomycosis, but on the other hand, widespread metastatic distribution and probable cerebral involvement speak for streptothricosis rather than for actinomycosis

Diagnosis from Examination of the Exudate or the Tissue without Culture—The etiologic agent in actinomycosis is found in the exudate or the tissue in the form of irregularly rounded or spherical, grayish or yellowish, compact granules containing a central mass of interlacing, branching, gram-staining filaments and peripheral, radially disposed, club-shaped, hyaline, refractive and eosin-staining bodies with a central filament In the case under discussion, granules of this character were found during life in the exudate from the lesions At postmortem examination the disease was much more extensive than was apparent during life In addition to the lesions already mentioned, there was involvement of the eighth and ninth dorsal vertebrae, purulent infiltration of the thoracic and lumbar, paravertebral tissue and abscess formation in the left, subphrenic region, the kidneys, spleen, liver, omentum, lungs, and the wall of the right ventricle Histologic examination showed the presence of organ-

isms chiefly in the form of compact filamentous colonies Typical club-shaped bodies with central filament were found about only one or two of the colonies

The evidence suggests that we are dealing here with actinomycosis from the presence of compact colonies of branching, gram staining, filamentous organisms with a peripheral zone of typical, club-shaped bodies The question may, however, be raised whether the findings are sufficiently distinctive to exclude some other infection as a cause of the disturbance In streptothricosis there is infection with branching, gram staining, filamentous organisms which are found in the exudate as isolated, slender, branching filaments, a loose network of filaments, or clusters or colonies of interlacing filaments The streptothrix group of organisms differs from actinomyces in the tendency to form loose rather than compact colonies and the absence in human infection of radially disposed, club-shaped, eosin staining, peripheral bodies with central filament The terminal portion of filaments may be club-shaped, but such are not true clubs in the sense in which this term is used with respect to actinomyces colonies Unlike actinomyces, organisms of the streptothrix group may be both acid and alcohol-fast, though less resistant to decolorization by these reagents than the tubercle bacillus

Such differences in morphology and in staining reaction are important in making a distinction between the two types of organisms as a cause of human infection, but there are limitations to the diagnostic value of examination without culture Actinomyces colonies are not always compact and with a radiate structure and are not always club-bearing, as is evident from the histologic examination in the case under discussion Certain strains of the streptothrix group are capable of forming compact, club-bearing colonies when inoculated into experimental animals Nakayama[1] produced club-bearing colonies by intraperitoneal inoculation of guinea-pigs with actinomyces asteroides (Eppinger) Cohn also produced club-bearing granules in animals with an aerobic, nonacid fast strain The illustrations

[1] Arch f Hyg 1906 Bd 58 p 207
[1] Centralb f Bakt 1913

accompanying these articles show club-shaped rather than true club-bearing filaments of actinomyces bovis In the case reported by Steele[1] a branching, filamentous, aerobic organism recovered from a cerebral and cerebellar abscess, inoculated into the rabbit's heart gave rise to inflammatory nodules in the lungs containing granules resembling those found in actinomycosis with radially arranged, peripheral, club-bearing filaments The club-shaped bodies, unlike those of actinomyces granules, were frequently pointed

Davis and Garcia[2] found definite, raylike bodies in abscesses in the ears and in the sections of tubercles in the lungs and peritoneum of rabbits, following inoculation with a pathogenic, acid-fast actinomycete (nocardia)

Naeslund[3] produced typical, club-bearing colonies by the inoculation of animals with organisms of the streptothrix group (act asteroides, act corneae, Str hominis) Club-formation was most pronounced following inoculation of rabbits into the anterior chamber of the eye and after intravenous injection in the lungs and kidneys, suggesting a selective action for certain animal tissues In his experience, also, the tendency to form clubs varied in different animals, being much more pronounced in cattle

It is evident that the tendency to form colonies or granules, with radiate structure and club-formation, is common to both actinomyces bovis and the streptothrix group of organisms This tendency is pronounced in human infection with actinomyces bovis, but appears to be absent in human infection with the streptothrix group with which, however, it occurs in inoculated animals So far as human infection is concerned, there seems little or no chance of error in making the diagnosis of actinomycosis when typical granules are present in the exudate or the tissue The diagnosis has usually been based on such findings, but our knowledge of the relation of branching, filamentous organisms to disease is limited and more complete identification

[1] Jour Med Res , 44, 1923, 1924, p 305
[2] Arch Dermat and Syph , vol 7, No 1, January, 1923
[3] Acta Path et Microbiologica Scand , 1931, Suppl VI

of the etiologic agent by observations of its cultural characteristics and the results of animal inoculation is desirable It should be appreciated in this connection that in cattle granules bearing clubs occur not only from infection with actinomyces bovis, but also with the actinobacillus of Lignières and Spitz as a cause of "woody tongue" Club-bearing granules are also apparently produced about dense, capsulated masses of Staphylococcus aureus infecting the udder of the cow and pig

The tendency of both actinomyces bovis and the streptothrix group to form colonies with radiate structure and club bearing filaments suggests a close relationship between them Differences in their behavior with respect to the developments of these characteristics appear to be due to environmental conditions It seems likely that virulence of the organisms and resistance of the host are the determining factors The relatively avirulent actinomyces bovis may be assumed to form compact, club-bearing colonies as a defence against the body fluids and cells, while the more pathogenic streptothrix group is capable of survival in loose aggregations, without the formation of club-bearing filaments

Isolation of the Actinomyces by Culture —Though actinomyces bovis infection of man can apparently be recognized by the demonstration in the exudate or the tissue of compact granules containing branching, gram staining filaments and radially disposed, club-bearing filaments, more complete identification by isolation in pure culture is desirable, to exclude the possibility that in man as in inoculated animals similar granules may occur as a result of infection with organisms of the streptothrix group

In the presence of contaminating organisms, isolation may be difficult or impossible. The granule should be washed by agitation in sterile salt solution or bouillon and this process repeated by transfer of the material through several solutions The granule should then be macerated on the inside of the test tube and a sample of the disintegrated material examined for filaments In the absence of filaments, it is useless to proceed further in the attempt at isolation If filaments are present, a

portion of the disintegrated material should be smeared on the surface of a number of plain agar plates Part of the plates should be incubated under anaerobic (McIntosh and Fildes method), others under aerobic conditions and the remainder kept at room temperature It is desirable, also, to make suspension cultures in melted 1 per cent dextrose agar cooled to about 40 C , by thoroughly distributing a part of the disintegrated material in test tubes filled to a depth of 7 to 8 cm Solid media has the advantage that in the presence of contaminations pure colonies of actinomyces may be found and transplanted to other media Bouillon cultures should also be made, but isolation in pure culture is difficult by this means in the presence of contaminations Clouding of the bouillon after incubation indicates the presence of a mixed growth By repeated washing in sterile salt solution or bouillon of parts of granules containing colonies of filaments, however, and thus separating the filaments from other organisms, pure cultures may at times finally be obtained in spite of the contamination

At the time of the postmortem examination, in the case under discussion, stab cultures in sugar agar and cultures on coagulated Loeffler's blood serum were made by J H Wright from the pus of abscesses in the liver, lung, abdominal wall and the subdiaphragmatic region and cultures on blood serum alone from the spleen and heart's blood The results indicate the facility with which pure cultures can be obtained in the uncommon instances in which there are few or no contaminating organisms Observation of the sugar agar stab cultures after incubation showed the development along the line of the stab in the deeper parts of the medium of a row of discrete, small colonies and only feeble growth in the upper part of the medium, from the material obtained from the liver, lung, abdominal wall, and right foot Microscopical examination of stained smears showed the presence of a pure growth of filamentous organisms in these tubes The cultures made at the same time on blood serum from these various abscesses as well as from the spleen showed the presence of a few unknown bacteria of different kinds The culture from the heart's blood showed no growth The stab

culture from the subdiaphragmatic abscess developed a mixed growth of bacteria

Wright obtained pure cultures of the organism from thirteen human and two bovine cases of actinomycosis often only after surmounting serious difficulties arising in consequence of the presence of abundant contaminating organisms In its biologic characters, the organism isolated by Wright was the same as that described by Wolff and Israel In addition to the confirmation of Wolff and Israel's findings, Wright made an important contribution in his demonstration of the production of true clubs about colonies of the organism immersed in such animal fluids as blood serum and serous pleuritic fluid

Of many observations since reported on the recovery of organisms of the Wolff Israel type from human actinomycotic lesions, those of Shiota[1] with a positive result in 28 of 39 cases Harbitz and Grondahl[2] in 20 or about 70 per cent of the cases, Dresel[3] in 7 of 11 cases and associated with organisms of the Bostrom type in two more, Colebrook[4] in 21 of 24 cases and Klinger[5] in over 30 cases are noteworthy

Cultural Peculiarities of the Actinomyces —The actinomyces is essentially an anaerobe Organisms recovered under partial or complete anaerobic conditions from actinomycotic lesions appear to belong to one species Growth in bouillon occurs at the bottom of the tube without clouding of the medium or surface growth Shortly after isolation the growth is in the form of coherent, whitish masses which under continued cultivation lose their coherent character and grow as a soft, friable, amorphous and somewhat viscid sediment at the bottom of the tube There are no essential differences in the growth in plain or sugar bouillon under aerobic or anaerobic conditions In suspension sugar agar cultures growth occurs after two to three days in the form of grayish white, irregularly spherical colonies,

[1] Deut. Zeit. f Chir 1909 101 289
[2] Beitr z path Anat u z. allg Path., 1911 50 193
[3] Ziegler s Beitr z path Anat u. z. allg Path *1914 1915 60 185*
[4] Brit Jour Exp Path 1920 vol. 1 197
[5] Centralb f Bakt. 1 Abt Orig., 1921 85 357

the development of which is most luxuriant in a zone several millimeters wide about ½ to 1 cm below the surface In the course of time and after repeated transplantation growth takes place also immediately under the surface No gas formation takes place Sugar agar stab cultures show growth, at first confined to the needle track ½ to 1 cm below the surface, and later at the surface and along the whole length of the line of inoculation

The cultural findings under aerobic conditions on slanted media differ with different observers In Wolff and Israel's hands surface growth under such circumstances was repeatedly absent or slow and seldom abundant Wright found the surface growth uncertain under either aerobic or anaerobic conditions Shiota found that with freshly isolated strains surface growth on agar slants was more abundant under anaerobic than aerobic conditions, and, yet, the reverse was often true In his experience, anaerobically isolated strains soon become accustomed to growth in the presence of oxygen Harbitz and Grondahl noted only very sparse or no growth on agar slants under aerobic conditions Dresel's strains failed to show surface growth under aerobic conditions All of Colebrook's strains showed a strong preference for anaerobic growth, but after frequent transplantation several became capable of some degree of aerobic growth Klinger observed a sparse surface growth under aerobic conditions with isolated strains In general, surface colonies are discrete and grayish-white, opaque, irregular or rosette shaped, with circular or irregular outline and elevated central portion Small colonies send rootlike projections into the medium, and show few or many radiating, branched and unbranched filaments under the microscope After repeated transplantation some strains show a white, moist, nongranular, confluent surface growth without projections into the medium No air hyphae are observed Spore formation has not been established

Transplantation of bouillon cultures should be made every seven to ten days Otherwise, strains may be lost The longest period of viability of Shiota's bouillon cultures was sixty to

seventy four days Viability in sugar agar is variable and may persist for as long as three months

Cultures of actinomyces are without odor Proteolytic action is absent Growth occurs at incubator and not at room temperature, if under 20 C

Morphology and Staining Reactions of the Actinomyces — Pleomorphism is a striking characteristic Microscopical preparations stained by Gram's method show branched or unbranched and longer or shorter bent rods due to fragmentation of filaments Their size and shape, though variable, is often much like that of the diphtheria bacillus, and, as with this organism, there may be deep staining points and areas in the protoplasm The terminal portions of filaments are at times swollen forming pear or olive-shaped extremities Club-shaped terminations of filaments in culture should be distinguished from the club bearing filaments or true clubs which develop about the colonies in human or animal tissue Actinomyces is not acid fast.

Results of Animal Inoculation with Anaerobic Organisms — In judging the etiologic relation of organisms of the Wolff Israel type to the disease, the results of animal inoculation with pure cultures are important Many failures to produce lesions in the smaller laboratory animals are recorded in the literature The largest measure of success was attained by Wolff and Israel Of 21 experimental animals, rabbits and guinea pigs, in their series inoculated for the most part intraperitoneally with pieces of agar cultures, 17 showed tumor growths histologically like actinomycotic tissue and with one exception containing typical actinomyces colonies and with radially disposed clubs in almost all instances

In the case under discussion, Wright inoculated 5 rabbits and 2 guinea pigs in various ways with the organism Only one animal, a rabbit, developed definite actinomycotic lesions This animal inoculated into the peritoneal and thoracic cavities, when killed after thirty four days, showed a firm peritoneal tumor about 10 mm in diameter and histologic examination of this tumor showed connective tissue and abscesses containing typical colonies, one with well-developed clubs

Animal experiments were made by Wright with cultures of the micro-organism from 13 cases Nearly a hundred animals (mostly guinea-pigs and rabbits) were inoculated, for the most part intraperitoneally, with a positive result in only about 30 per cent All of his 13 strains, however, produced typical, club bearing colonies in the animal tissues In Shiota's experiments with 24 strains on 100 animals (rabbits) pathologic changes were produced in a large proportion of the inoculations In general, pure cultures of organisms of this type fail to produce a progressive disease in these experimental animals and it is improbable that multiplication of the organisms occurs within the tissues of the animals By the inoculation of cattle, however, Naeslund[1] was successful in the production of true actinomycosis by subcutaneous inoculation with pure cultures of organisms of the Wolff-Israel type derived from human actinomycosis

[1] Acta Path et Microbiologica Scand , 6, 1929

CLINIC OF DR WILLIAM H ROBEY

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THROMBOSIS IN THE ABDOMINAL VISCERA

PHYSICIANS and surgeons are confronted with the problem of thrombosis of the mesenteric viscera after surgical operations and during the management of various diseases, especially the cardiac and circulatory disorders, which taxes their powers of diagnosis to the utmost For many years the writer has been interested in this question—one which you will be called upon from time to time to settle and which you will find very difficult because your decision must be reached quickly and your action promptly

There are two types of cases, the acute and chronic. In the acute cases the onset is often sudden with agonizing pain, nausea, vomiting, bloody diarrhea, and the symptoms of acute obstruction It may follow acute appendicitis, pelvic infection or occur in the course of cardiac diseases, especially mitral stenosis or subacute bacterial endocarditis It may also occur in cachectic conditions In the chronic cases the onset is often insidious and, as Osler states, there may be no symptoms referable to the abdomen The occurrence, however, of sudden, severe, abdominal pain with some or all of the above mentioned gastro-intestinal symptoms, especially in a patient who has arteriosclerosis or the history of infarctions in other areas, should suggest thrombosis or embolus of the mesenteric vessels In a patient who has already had thrombosis of the cerebral or coronary vessels the sudden onset of severe, agonizing pain in the abdomen with attendant gastro intestinal symptoms should lead to a diagnosis of thrombosis of the abdominal viscera

On the contrary, in a case of subacute bacterial endocarditis followed for several months with Louis J Ullian, the patient had repeated evidence of emboli in various parts of the body, such as the spleen, kidneys, liver, and skin, and, while sudden, severe pain occurred whenever emboli lodged in any of the viscera, the abdominal vessels escaped, but had an embolus entered a mesenteric vessel we would have recognized its presence because we were constantly on the watch for new embolic localizations In the chronic form the onset is usually less severe and is most apt to occur in those cases showing signs of circulatory degeneration

DIAGNOSIS

The diagnosis of thrombosis of the mesentery is extremely difficult Thrombosis of the heart and brain are well recognized but thrombosis of the abdominal viscera, especially of the mesenteric vessels, is often missed If thromboses have occurred elsewhere we should have the possibility in mind when sudden and agonizing pain occurs in the abdomen If the patient has mitral stenosis, subacute bacterial endocarditis or a septic lesion of the abdominal cavity the sudden appearance of abdominal pain should at once suggest the possibility of thrombosis As Dr Conner says in a recent article,[1] the failure to recognize attacks of arterial thrombosis in the abdominal organs must be due in part to the inherent difficulties of diagnosis but is almost certainly also due to one's failure to have the possibility of such attacks in mind Certain symptoms of thrombosis are common to many viscera, brain, heart, spleen, kidney, and leg vessels All are characterized by pain and loss of function Often there is a large group of patients who have thromboses without symptoms, or there may be a mild degree of abdominal symptoms which pass in a few hours or days and are recognized because of cardiac or other blood vessel pathology

In the acute group, which is the larger, the onset is often sudden with colicky pain, sometimes sharp and agonizing, nausea, vomiting, sometimes bloody and fecal in character, and diarrhea, often bloody In some of our protocols it will be seen

that the attack was preceded for several days by obstinate constipation which cathartics and enemata failed to relieve In some the symptoms may abate for a few hours only to return with greater violence There are signs of collapse, thready pulse, cold perspiration, subnormal temperature, abdominal distention, tenderness, and rigidity

In the lesser or chronic group the symptoms are rarely as violent and the course longer and more varied according to the degree of occlusion

In our autopsy records there is some differentiation between occlusion of a mesenteric artery and vein, but the former far outnumbers the latter Clinically and pathologically there is very little difference Physical signs and pathologic damage bear a marked similarity in either state

Intestinal obstruction is one of the commonest accompanying conditions of mesenteric thrombosis and progresses rapidly in many cases Other causes of obstruction, such as intussusception, volvulus, bands, gallstones or cancer, must be considered Diseases causing blood in the stools or vomitus must be excluded, such as duodenal or gastric ulcer, heart and liver diseases Rules have been given for the differentiation of the various forms of pathology of mesenteric thrombosis but they are full of flaws

Jackson, Porter, and Quinby[2] cite the experiments of Cohnheim, Litten, Cohn, and others which show conclusively that the results of a stoppage of blood supply to the intestine are divided into four stages first, necrosis, second, gangrene, third, hemorrhagic infarction, fourth, abscess formation

Pathologically, occlusion of the mesenteric vessels was described by Virchow in 1847 but the clinical picture was first called to the attention of physicians by Litten in 1875 According to Ribbert[3] in contrasting the intestine to the kidney, brain, and spleen in which there is generally an anemic infarct it is different in occlusion of the superior mesenteric artery which always causes hemorrhagic infarction. There are present anastomoses with other vessels but these do not suffice for nutrition but carry so much blood to the excluded area that it is made

turgid and diapedesis takes place Then the gut wall and mesentery become black-red and thickened by the mass of blood Similar hemorrhagic infarction occurs also from venous stasis

Low blood pressure, slowing of the heart's rate and changes in coagulation time must be factors in the production of thrombosis in arteries and veins Certain metabolic disturbances little understood at the present time are undoubtedly predisposing causes

TREATMENT

Domanig[4] thinks that since the incidence of venous thromboses and thrombo-embolisms has increased considerably in recent years more effort should be made to determine whether a patient has a predisposition to thrombosis and, if so, to take suitable prophylactic measures As predisposing factors for thrombosis he mentions local retardation of the blood stream, resting position, old age, cardiac and circulatory disturbances, and adiposity Changes in the blood and changes in the endothelium of the vascular walls are probably of great importance He advocates measures that will favorably influence cardiac and circulatory action and counteract the localized retardation of the blood stream Circulatory disorders should be counteracted by medication with digitalis or with ephedrine and excitants Systematic respiratory exercises, massage, gymnastics, and frequent changes in the position of the patient are also advisable Constipation should be counteracted Early rising after an operation as a preventive is not favored

Bancroft and Stanley-Brown favor a régime which in 4250 operations has resulted in freedom from death from postoperative thrombosis Three deaths have occurred from embolism in private practice of members of the staff who have not carried out these principles of treatment These authors believe that loose abdominal dressings, early postoperative feeding and fluid administration relieve postoperative distress and may diminish thrombosis Blood studies show that certain individuals are more prone to develop thrombosis than others It is their belief that in a number of cases thrombosis and embolism may be aborted by administering a diet low in fats and proteins and

by the intravenous use of sodium thiosulphate, although they are not satisfied that this drug offers the best means of approaching the problem but it seems the best aid at present

Diet, metabolism, and blood clotting time have been the lines which clinicians have followed recently in an effort to solve this problem The surgeons particularly interested in blood vessel diseases with whom I have discussed such measures express grave doubts of the value of these or any other methods After all, are they not followed by most clinicians in treating cardiac, circulatory, and metabolic disorders? Is it possible in the brief time that a patient is in the clinic waiting for operation to carry out any procedure which will be of value in the prevention of postoperative thrombosis or embolism? Hundreds of patients with grave circulatory disorders are operated upon each year without mishap, yet this is no argument against vigorous attempts to find a method which will safeguard even the few However, the condition is extremely rare Jackson, Porter, and Quinby (loc. cit) were able to collect from all the Boston hospitals professional friends and the literature but 214 cases A thorough search of our Boston City Hospital records discloses 51 cases covering a period of thirty three years and including all types Doubtless there were more which never gave any recognizable symptoms and were either discharged, relieved or never came to operation nor autopsy It is interesting to note that 27 of our 51 cases were of medical origin leaving 24 surgical and only 13 where mesenteric thrombosis followed operation and of these 6 were cases of acute appendicitis or peritonitis Septic infarcts caused by emboli are apt to form in these cases whether there is an operation or not. In the total number of all cases treated during these thirty three years were 162,574 medical and 206,571 surgical

In view of the recent statement of two authors that about 4000 operations were performed after special prophylactic measures had been instituted without a single case of mesenteric thrombosis, it is intersting to note that there have been years in this hospital when no cases occurred either medical or surgical, as, for instance, in 1912 there were 4425 medical and

Year	Sex	Age	Clinical history	Clinical diagnosis	Anatomical diagnosis	Duration	Result
1898	M	47	5 months of dyspnea and orthopnea followed by edema of the ankles, no abdominal symptoms	Chronic nephritis, general arteriosclerosis	Dilatation of heart, chronic passive congestion of liver and spleen, chronic diffuse nephritis, general arteriosclerosis thrombosis of branches of the superior mesenteric artery	No abdominal symptoms	Died
1900	M	56	Came in for dyspnea, edema of the legs and cardiac failure, later developed an incarcerated hernia Poor condition contraindicated operation	Incarcerated hernia	Intestine greatly distended above a point about midway in the ascending colon where there is a volvulus, superior mesenteric artery occluded by a dark red blood clot the descending branch of left coronary artery contained a clot of pale red color, many infarcts of kidney	Hernia obscured other abdominal signs.	Died
1901	M	44	Symptoms at entrance of dyspnea and cardiac failure, no abdominal symptoms	Myocarditis patent foramen ovale	Thrombus of pulmonary artery and of right auricle with extension to left auricle through patent foramen ovale, embolus of left renal artery, both iliac arteries, superior mesenteric hepatic, splenic, innominate and carotid arteries, infarct of spleen intestine and kidneys, acute softening in the left occipital lobe of the cerebrum.	No abdominal signs	Died
1902	M	25	Pain in back, sides and arms for 3 weeks in bed 2 weeks, 1 week of pain and tenderness in lower abdomen, some dyspnea and palpitation on exertion decreased urination	Chronic nephritis arteriosclerosis coronary sclerosis	Coronary arteriosclerosis multiple thromboses of heart, pancreas and liver hemorrhage from thrombosed area of liver into peritoneal cavity	1 week	Died
1902	M	21	Abdominal pain and vomiting with chills No cause found	Infarct of intestine peritonitis	Acute abdomen peritonitis	5 days	Died
1901	M	35	Heavy drinker 2 weeks before entrance troubled by cough and abdominal pain, only remedy whisky, physical signs of pulmonary tuberculosis	Phthisis, alcoholism	Embolus of pulmonary, innominate and superior mesenteric arteries, tuberculosis of right lung patent foramen ovale infarcts of kidney, edema of pia	2 weeks	Died

1906	M	23	*Headache for 5 days, fever sleeplessness, enlarged and rapid heart, petechiae over body temperature 105 F pulse 130.*	*Malignant endocarditis.*	Acut and chronic endocarditis; chronic pericarditis and pleuritis; thrombosis f branches of mesenteric artery Gastro-intestinal tract normal save for 5 areas along small intestine which are dark in color and near the mesenteric attachment the vessel supplying that part contained a firm adherent clot	No abdominal symptoms.	Died.
1907	F	30	Always well until attack of abdominal pain which lasted 1 week; dark colored vomitus for 1 day before admission	Mesenteric thrombosis	Three-fourths of small intestine slightly distended, chocolate-colored edematous thrombosis of superior mesenteric vein and portal vein infarct and gangrene of small intestine· acute local peritonitis.	1 week.	Died.
1907	F	38	Pain in abdomen frequent vomiting, alternating constipation and diarrhea.	Mesenteric thrombosis.	Acute, perforated, gangrenous appendix, retroperitoneal abscess.	5 days.	Died.
1909	F	36	Heart trouble for 5 years, recently "run down" fever no appetite headaches transitory pains in joints, numerous petechiae	Malignant endocarditis cerebral mesenteric and iliac thromboses	Moderate arteriosclerosis chronic ulcerative endocarditis streptococci of valves and emboli embolus of right colic branch of superior mesenteric artery and right common iliac artery	3 months.	Died.
1910	M	82	Sudden, severe abdominal pain 48 hours before entrance moderate abdominal distention and diffuse tenderness, bowels moving normally immense amounts of dark colored vomitus, heart intermittent and otherwise negative Died on day of admission.	General peritonitis and ruptured appendi	Infarcts of large and small intestine embolus and thrombosis of superior mesenteric artery· arteriosclerosis *Jejunum in upper 130* cm slightly congested 5 cm. below hepatic flexure there is again a sharp line of demarcation	2 days.	Died
1913	M	76	For 3 weeks vertigo and syncope chills, fever swelling agonizing pain in abdomen and chest for 4 days no jaundice, no vomiting On physical examination the head heart, and chest were essentially negative abdomen showed moderate spasm and tenderness in the right lower quadrant near the costal margin	Indefinite Perinephritic abscess pus in the gallbladder and liver abscess were considered	Thrombophlebitis of the superior mesenteric and portal veins multiple abscesses of the liver chronic localized peritonitis arteriosclerosis and sclerosis of the mitral and aortic valves and the aorta. *Heart's blood contained the* streptococcus pyogenes.	3 weeks.	Died.

Year	Sex	Age	Clinical history	Clinical diagnosis	Anatomical diagnosis	Duration	Result
1914	M	59	Rheumatism 7 years ago just before admission discharged from the Peter Bent Brigham Hospital with a diagnosis of bronchitis and carcinoma, almost moribund with extreme emaciation and inability to swallow	Pulmonary tuberculosis	Carcinoma of esophagus, arteriosclerosis mesenteric thrombosis	No abdominal symptoms	Died
1916	M	60	3 days before entrance feeling of depression after long period of constipation vomited for 3 days foul smelling and suggestive of blood Operation Bowel thickened infected mesentery thrombosed and large vessels involving about a foot of mesenteric	Intestinal obstruction	No autopsy	7 days	Died
1916	M	58	45 years ago had similar attack 5 days before entrance abdominal cramps vomited 2 days after onset following ingestion of considerable rum bowels moved daily with saline laxative Operation Cloudy fluid in peritoneum appendix injected marked inflammatory condition in intestine probably due to mesenteric thrombosis mesentery friable and dark	Mesenteric thrombosis general peritonitis acute appendicitis	No autopsy	5 days	Died
1916	M	23	At home 2 weeks with severe tonsillitis abdomen tender spastic rigid Operation Abdomen full of yellow serum with fecal odor no appendix involvement stomach perforation nor gallbladder disease Died the following day	Tonsillitis septicemia mesenteric thrombosis	No autopsy	2 weeks	Died
1917	M	46	Gradual distention of abdomen with pain vomiting, becoming fecal in character Operation for a strangulated hernia patient died next day of mesenteric thrombosis The whole of small intestine was dark blue and gangrenous	Mesenteric thrombosis, alcoholism delirium tremens	No autopsy	1 day	Died

1917	M	47	Operation on day admitted bowel retrocecum swollen, tense, ready to perforate, temperature and drainage of pus from wound. *x* Ray shows right diaphragm from left suggestive of subphrenic abscess or abscess of liver	Appendicitis; mesenteric thrombosis; pyelonephritis; multiple abscesses of the liver	Appendicitis mesenteric thrombosis; pyelonephritis multiple abscesses of the liver	?	Died.
1917	M	35	Said to have been caught between a truck and freight car sustaining injury to abdomen considerable shock, abdomen soft, level and slight tenderness in lower quadrants especially the left, condition remained the same for 8 hours when abdomen became sharply distended; pulse rate increased with pain and tenderness in lower quadrants abdomen opened, large amount of old blood 3 feet of bowel black.	Abdominal injury and shock.	No autopsy	?	Died
1917	M	48	Dyspnea and orthopnea, cough with small amounts of sputum, night sweats, temperature 98 to 106 F respiration 20 to 40 pulse 80 to 140, white count 8000 blood smear negative, blood culture streptococci, patient stuporous throughout, abdomen distended, diarrhea	Streptococcus tonsillitis septicemia acute peritonitis.	Gangrenous and perforated appendix, localized peritonitis with abscess formation septic thrombi in mesenteric and portal veins with abscess.	?	Died.
1918	M	65	Abdominal tenderness, small palpable mass over left upper quadrant, no special spasm these symptoms increased. Operation advised. The patient died before operation could be performed	Cerebral hemorrhage thrombosis of the mesenteric vein.	No autopsy	5 days.	Died.
1918	F	34	Immediate operation 10 feet of ileum and jejunum distended, atonic and practically dead. Too much bowel affected to consider resection; no cause found.	Intestinal obstruction	No autopsy	?	Died
1919	F	16	2 days after entrance very marked cyanosis and dyspnea, marked abdominal distention, constant vomiting of fecal matter Mesenteric thrombosis the most probable diagnosis.	Influenza, bronchopneumonia mesenteric thrombosis.	No autopsy	4 days.	Died.

Year	Sex	Age	Clinical history	Clinical diagnosis	Anatomical diagnosis	Duration	Result
1919	M	33	The day before death, having recovered from *pneumonia* he became greatly distended which increased during the day began to vomit, fecal and bloody, generalized tenderness, spasm marked distention Apparently a mechanical obstruction due to *mesenteric thrombosis*	Lobar pneumonia, alcoholism, *mesenteric thrombosis*	No autopsy	12 hours	Died
1919	M	58	Entered Medical for vomiting and distention Transferred to Surgical, operation and death all on same day	Intestinal obstruction with question of carcinomatous mass	No autopsy	?	Died
1919	M	53	Operated on November 21st and gallbladder removed The convalescence was satisfactory up to December 8th when he was allowed to sit up, became suddenly ill with bloody vomitus and bloody fluid in the feces *December* 16th operation Died same day	Evidences of pathologic gallbladder	Carcinoma of the pancreas fat necrosis of pancreas, thrombosis of portal and splenic veins and of several branches of the mesenteric veins	7 days	Died
1920	F	48	Chronic cardiac decompensation with many admissions to hospital Hypertension pulse deficit and considerable coffee ground vomitus	Chronic myocarditis, mitral insufficiency auricular fibrillation chronic nephritis	Arteriosclerosis mesenteric thrombosis, fibrous myocarditis	No abdominal symptoms	Died
1920	F	36	Always constipated 3 days of severe pain in abdomen, no movements with various cathartics, continuous greenish vomitus with very acute pain At operation numerous adhesions and gangrene of small intestine Died 4 days later	Mesenteric thrombosis	No autopsy	1 week	Died
1922	F	60	Severe lower abdominal pain for 60 hours, vomiting and constipation, referred to Surgical Service 5 hours later 3 days of severe	Intestinal obstruction	Intestinal obstruction gangrene of bowel mesenteric thrombosis general peritonitis	3 days	Died

			abdominal pains, generalized and colicky abdomen distended throughout, no masses, temperature 100 F., respirations 22, pulse 120. At operation 12 inches of intestine caught in a single band of adhesions, black and gangrenous, not returning to good color				
1922	M	78	No abdominal symptoms symptoms of arteriosclerosis chronic heart disease; hemiplegia.	Cerebral hemorrhage; mental symptoms and paralysis.	Small intestine dark reddish-black; superior mesenteric artery thrombosed, infarct of small intestine chronic vascular nephritis marked arteriosclerosis.	No abdominal symptoms.	Died.
1923	M	69	For 4 or 5 years until 6 months ago epigastric pain 30 minutes after meals, relieved by baking soda. Past illness, dyspnea and edema of ankles.	Arteriosclerosis myocardial insufficiency mesenteric thrombosis.	Mesenteric thrombosis of vein.	No abdominal symptoms	Died.
1923	M	74	Entered July 30th On August 5th had sharp abdominal pain with vomiting with several recurrences, bowel palpable Operation advised against.	General arteriosclerosis pericarditis bronchopneumonia thrombosis of superior mesenteric artery	Adhesive pericarditis arteriosclerosis thromboses of superior mesenteric artery and right gastro-epiploic artery gangrene of small and part of large intestine chronic pulmonary tuberculosis with cavitation adhesive pleuritis.	12 days.	Died.
1923	M	42	3 or 4 attacks of abdominal pain in 6 months; 1 day before admission epigastric pain, distention and vomiting comfort for a few hours and then return of symptoms. At operation thickened appendix with thickened and friable mesentery	Acute appendicitis with perforation ? of mesenteric thrombosis.	No autopsy	3 days.	Died.
1924	M	42	Chief complaint: pain in abdomen for 1 week pain started at umbilicus spreading to both sides; induced vomiting no blood, no blood in stools, small hematoma in the mesentery which seemed to be due to the twisted gut rather than thrombosis. Died. A large portion of the ascending colon was black and gangrenous.	Mesenteric thrombosis volvulus	No autopsy	1 week.	Died.

Year	Sex	Age	Clinical history	Clinical diagnosis	Anatomical diagnosis	Duration	Result
1924	F	38	For 4 or 5 years dyspnea on exertion, edema of the feet and ankles some constipation for 2 years spells of nausea and vomiting during which there have been attacks of abdominal pain in the upper right quadrant Examination Tenderness and spasm of the right lower quadrant with a history of attack in the right lower quadrant Operation Free fluid in abdominal cavity Exploration showed normal uterus and tubes slightly drawn to the right where there is a mass gangrene of cecum, lower 3 inches rapid incision of gangrenous area, purulent discharge from wound during her entire stay at hospital Discharged to her own physician	Mesenteric thrombosis gangrene of cecum		24 hours	Relieved
1924	M	53	Symptoms of acute infection, no abdominal symptoms	Subacute bacterial endocarditis	Thrombosis of ileal branch of mesenteric artery infarct of ileum heart's blood streptococcus viridans	No abdominal symptoms	Died
1924	M	54	Operation for hemorrhoids 3 days after entrance, 2 days later abdomen distended no vomiting, 2 days later marked cyanosis abdomen greatly distended, slight tenderness over the liver No operation for thrombosis Discharged dead	Hemorrhoids mesenteric thrombosis	No autopsy	3 days	Died
1925	F	26	Operation for cervicitis Day after entrance had appendectomy from which she made good recovery 1 week later she seemed as well as usual but started to vomit projectile in type but not fecal some	Chronic endocervicitis thrombosis of mesentery	No autopsy	1 day	Died.

			epigastric distention. Enterostomy was done but the patient died in about a half hour. A postoperative examination of the wound showed coils of distended small intestine; there was a point of necrosis in the ileum several feet from the cecum with a spot of corresponding thrombosis in the mesentery below this point the intestine was completely collapsed, there being apparently a spastic ileus at the point of necrosis.				
1925	F	71	Vomited 6 times at onset, no jaundice nor abdominal pain clay colored nor bloody stools abdomen soft and tympanitic throughout except in right upper quadrant and right flank where there was a rounded palpable mass not tender	Chronic nephritis bronchopneumonia.	Mesenteric embolism and thrombosis.	No abdominal symptoms.	Died.
1925	M	67	Admitted August 10th with symptoms of intestinal obstruction, and immediately transferred for operation. Operated on and died next day	Mesenteric thrombosis arteriosclerosis.	No autopsy	9 days	Died.
1925	M	36	Admitted for rheumatic heart disease on October 5th. On January 15 1926 when about to be discharged developed abdominal distention with vomiting of all food after attack subsided barium series failed to show pathology	Rheumatic heart disease aortic regurgitation mitral stenosis cardiac decompensation mesenteric thrombosis?		3 days.	Relieved.
1925	M	62	Admitted July 23rd for chronic heart disease August 3rd sudden abdominal pain with rigid abdominal wall. Surgical consultant advised morphia and delay. Attack quieted down and was followed by several milder ones.	Chronic myocarditis mesenteric thrombosis.		2 weeks.	Relieved.

Year	Sex.	Age	Clinical history	Clinical diagnosis	Anatomical diagnosis	Duration	Result
1926	F	62	In good health until January 15th Admitted January 16th. General physical examination satisfactory, marked pain, tenderness and spasm over entire abdomen without definite localization Immediate operation Free serosanguinous fluid upon opening peritoneum, normal appendix and gallbladder, 3 feet of small intestines deeply congested and reddened, gangrenous for 10 inches Died on January 17th	Intestinal obstruction	Infarct of spleen, mesenteric thrombosis	3 days	Died
1927	M	13	Entered moribund with a history of heart disease for many years abdomen distended and tympanitic. Died shortly after admission.	Pericarditis with effusion rheumatic heart disease, congenital heart disease mesenteric embolus	No autopsy	?	Died
1927	M	74	Well until day of onset when he had sharp, sudden pain in right iliac region with vomiting	Bronchopneumonia, general arteriosclerosis senility, ? of mesenteric thrombosis	No autopsy	1 day	Died
1928	M	60	Symptoms of acute appendix May 7th, died May 8th following operation	General peritonitis mesenteric thrombosis.	? of mesenteric thrombosis	1 day	Died.
1929	I	73	For 3 weeks vomiting after each meal, abdominal soreness, severe constant pain in rectum, bowels regular with cathartics, a similar attack 7 years before. Physical examination General abdominal tenderness painful rectum with very hard mass, probably fecal oil enema and oil by mouth with slight result.	Malignancy of gastro-intestinal tract stomach and rectum, syphilis	Malignant adenoma of intestinal tract with metastasis to liver and lung carcinoma of liver, thrombosis of superior mesenteric artery gangrene of small intestine	?	Died
1930	F	35	Severe rheumatic fever in childhood Developed abdominal pain vomited, transferred from Medical to Surgical but died on day of admission without operation, abdomen distended with large, tender mass in left upper quadrant	Mesenteric thrombosis, mitral stenosis auricular fibrillation left hemiplegia	Mesenteric thrombosis infarcts of brain spleen and kidney	1 day	Died

1930	F	60	After being up at end of third week, suffered a sudden attack of abdominal pain with vomiting. Surgical consultant advised against operation.	General arteriosclerosis; hypertensive heart disease; auricular fibrillation mesenteric embolus cerebral embolus cardiac decompensation thrombosis of left femoral artery	No autopsy	2 days.	Died
1940	M	35	Admitted October 18th with advanced rheumatic heart disease. Discharged dead on December 19th but just before death had abdominal pain, distention, vomiting; condition did not permit operation.	Rheumatic heart disease aortic and mitral stenosis and regurgitation mesenteric infarct?	Autopsy showed bloody intestines but no thrombus nor embolus was found	A few hours.	Died.
1931	M	63	Admitted with lower abdominal pain sigmoidoscopy without improvement.	Carcinoma of rectum with liver metastases pulmonary embolism phlebitis.	Embolus of pulmonary artery; thrombosis of branches of femoral and mesenteric veins, arteriosclerosis carcinoma of sigmoid with metastases to liver	No abdominal symptoms indicating thrombosis.	Died.

5490 surgical cases admitted to the wards without a single instance of mesenteric thrombosis which could be recognized by any of the methods at our command The following table will indicate the various types of cases and their causes

Medical		27
Surgical		24
Operation followed by mesenteric thrombosis		13*
Operation for mesenteric thrombosis		11
Multiple infarcts		7
Multiple infarcts of infectious origin		5
Causes		
Acute appendicitis	6	
Cancer of G I tract	4	
Acute tonsillitis	1	
Phthisis	1	
General arteriosclerosis	15	
Acute cardiac disease	3	
Acute pneumonia	2	
Hemorrhoids	1	
Chronic cardiac disease	8	
Intestinal obstruction	7	
Unknown	4	
No abdominal symptoms		10
Autopsy		31
No autopsy		20
Relieved		3†

* In this group there were but 2 cases where thrombosis followed a clean operation, one for hemorrhoids and the other for appendicitis in which the patient appeared to be making a satisfactory recovery In the other cases there was a septic condition and mesenteric infarcts occurred either before the operation, coincidentally, or immediately following it and could not be considered as a direct sequel of the operative procedure

† Of the cases discharged relieved, one was a successful operation with resection of the bowel, one was a chronic thrombosis in a patient with advanced arteriosclerosis and one in a case of rheumatic heart disease

Jackson, Porter, and Quinby reported 47 cases operated upon with 4 recoveries In their series of 214 cases 14 of these, largely of the chronic group, recovered

The only form of treatment which is of any avail is immediate operation, as soon after the diagnosis is made as possible Great discretion is necessary, however, in the selection of cases suitable for operation In cases of apparent intestinal obstruction where the cardiac, circulatory, and other physical

findings are reasonably satisfactory, operation should be done at once with the hope that the obstruction may be the result of some one of the other causes of that condition In advanced cases of arteriosclerosis and cardiac disease where thrombosis is most common and where multiple infarcts are not infrequent the results of operation are well nigh hopeless and it requires the combined discrimination of internist and surgeon to decide upon a step which offers little prospect of recovery Again cases occurring in the course of a profound bacteremia as in subacute bacterial endocarditis, pneumonia or an advanced appendicitis offer little hope because of the feeble state of the patient at the time of the mesenteric accident and the probability of multiple septic infarcts

Five cases of appendicitis in our series were all of this type.

I wish to express my thanks to Dr F B Mallory and members of the Visiting Staff of the Boston City Hospital for the privilege of reporting these cases

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CLINIC OF DR REGINALD FITZ

PETER BENT BRIGHAM HOSPITAL

A CASE OF THORACIC ANEURYSM

TODAY, I propose to hold an old fashioned clinic, beginning with the presentation of a patient's history and physical findings, next demonstrating the essential pathology that produced this history and these findings, and finally ending with a general discussion in regard to the diagnosis, prognosis, and treatment of the disorder from which the patient suffered Thoracic aneurysm is the subject I have elected to take up in this fashion

Mr X a consulting engineer sixty years old came to the hospital for examination on March 25 1925 seven and a quarter years before his death His complaint was pain in the chest and back which had been disturbing him for about nine months.

He was a well-educated man who had traveled all over the world. In 1893 when he was twenty-eight years old and lacking in discretion he had acquired syphilis This had been recognized early and had been treated in the fashion of the day with mercury and iodide. He had suffered no ill effects from the disease and had spent a busy active life doing desk work rather than field work and suffering no physical ailments. Two years after the primary lesion was treated his doctors had considered it proper for him to marry His wife and 2 children are now living and well. One child had died at birth There had been no miscarriages

About eight months before his first visit to the hospital he developed a pain like a toothache under the left shoulder blade. This pain had persisted in an intermittent fashion coming in attacks always starting in the back, apt to radiate around to the front of the chest, appearing either by day or night and at times so severe as to make him feel as though his chest was being gripped in a vise. The pain was not referred to either arm nor was it brought on by exertion He considered that he was no shorter of breath than were most of his contemporaries. He had no cough

During the past eight months the pain had grown worse little by little. He had consulted various doctors who had told him that he had neuritis and he had experimented by way of treatment with an electrical vibrator or heat in various forms. He had concluded that whatever produced his

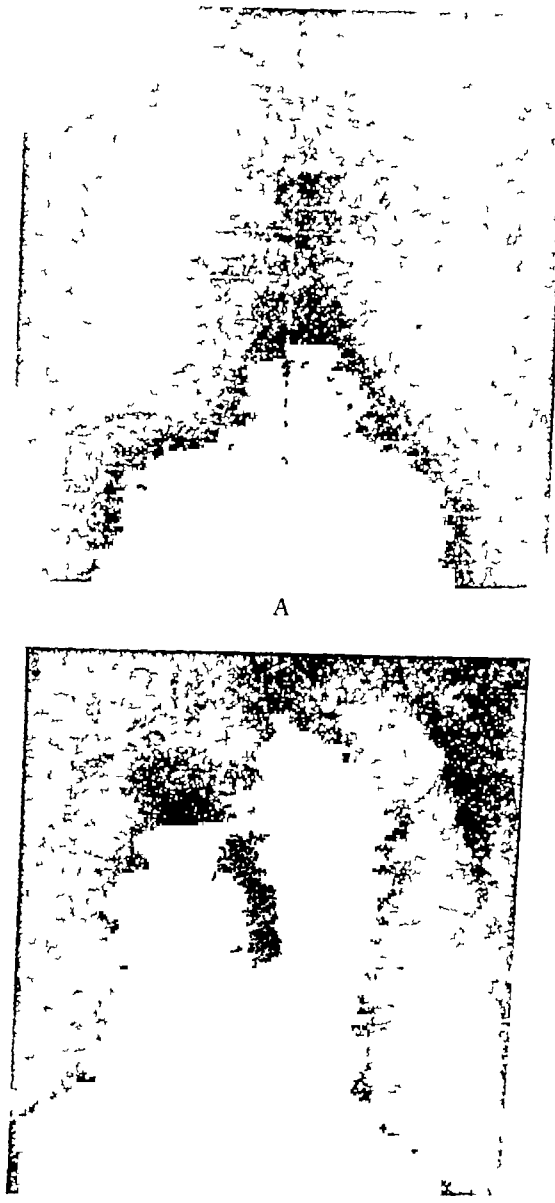

Fig 159 —x-Ray films (anterior and oblique views) of thoracic aneurysm

backache was not amenable to such treatment, and, therefore, he had made up his mind to attempt to go further in the matter of finding what was so wrong with his chest as to make him feel as he did

He had been losing a little weight very gradually over a period of several years. But his appetite and digestion seemed normal he slept well except when pain disturbed him and he had no symptoms to focus his attention upon the genito-urinary tract In brief what he wanted was to find the cause of his pain and to be rid of it

He was 5 feet 6 inches tall and weighed 139 pounds The pupils were equal and reacted normally The heart was not enlarged to percussion though the retrosternal dulness was markedly increased There was a visible pulsation over the entire upper chest which caused an expansile heave rather

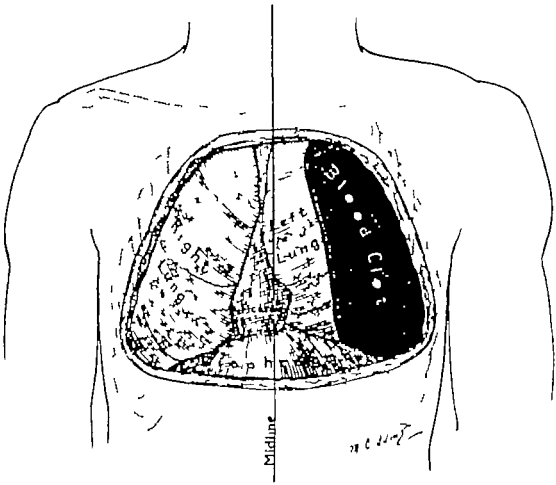

Fig 160 —Sketch of appearance of thoracic cavity in a case of ruptured thoracic aneurysm

than the simple thrust that is seen in association with cardiac hypertrophy No pulsation was visible over the back.

The heart sounds were of good quality and noteworthy in two respects There was a faint blowing systolic murmur to be heard over a small area in the third right interspace close to the sternum Over this area no thrill was to be felt, but the second heart sound here had a metallic snapping note which was remarkable in the face of a normal blood pressure level

The blood pressure was 130/70 in each arm the pulse rate was 80 There was no peripheral edema and no signs of lung or liver congestion There was no tracheal tug

The voice and breath sounds over the left upper lobe were muffled and had a nasal twang, perhaps suggesting compression of the bronchial tree In other respects the physical examination was negative.

x-Ray examination of the chest revealed a heart of normal size and shape, but an aorta that was markedly widened and which showed two separate dilatations, one in the region of the arch of the aorta and the other in the region of the descending portion These dilatations pulsated, as one could see by fluoroscopy, and appeared due to two separate aneurysms

The Wassermann reaction was strongly positive

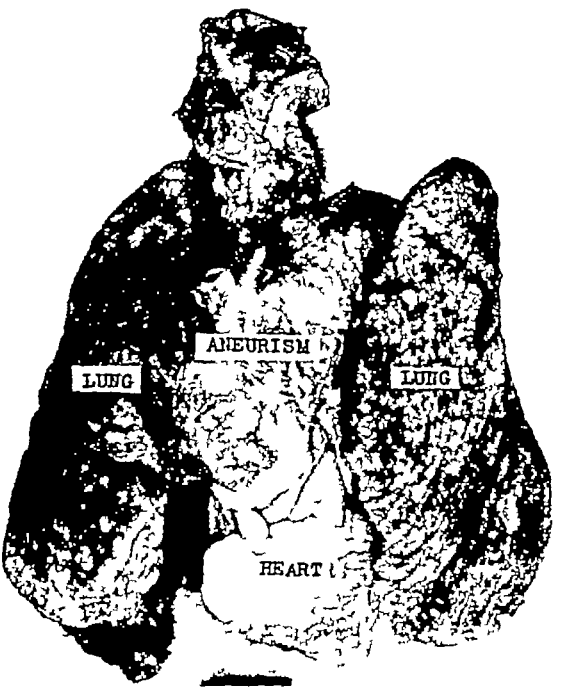

Fig 161 —Photograph of thoracic aneurysm (anterior view)

The patient got along very comfortably for more than seven years after this examination I shall discuss the treatment employed and its results a little later

In June, 1932, while he was working in his garden he felt a new kind of pain, one "that traveled all around his arms, chest, and stomach" He thought that he had the grippe, took his temperature, and found that he had a slight fever After a few days' rest he was more comfortable and able to visit the hospital My note on this occasion says 'He continues to look very well and to have signs that change very little The aneurysm, anteriorly, is easily to be felt I think it is getting nearer to the surface than ever The heart is little if any enlarged The breath sounds at the left apex are

not well heard and perhaps are exaggerated on the right. There are a few fine crackles at the left apex. I hope he has had an acute infection and is not having pressure symptoms. He attended business that afternoon spent a fairly comfortable night listened to the radio on the following morning suddenly had very severe pain in his chest and died almost instantaneously

The Pathology —On opening the thorax there appeared to quote Ambroise Paré a great quantity of blood powred forth into the capacity of the chest. The heart and mediastinum were pushed far over into the right half of the thoracic cavity by masses of blood and blood clot in the left chest and the left lung was collapsed and shrunken The sketch of these findings

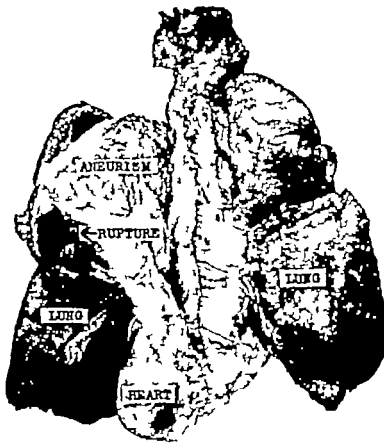

Fig 162 —Photograph of thoracic aneurysm (posterior view)

gives you some idea of the very striking appearance that may be presented by a ruptured thoracic aneurysm

The heart was of normal size. The ascending arch of the aorta was dilated in a saccular fashion and presented anteriorly The dilatation extended to the transverse portion of the arch and involved it also At the junction of the transverse and descending portions of the aorta, there was a slight narrowing below which again was a second larger saccular dilatation of the upper portion of the descending aorta. This ended fairly sharply, leaving the lower descending aorta of approximately normal size.

The aneurysm of the ascending and transverse aorta was fairly thick walled and there had been deposited in it a considerable amount of laminated

calcified blood clot The aneurysm of the descending aorta was thin walled and had finally ruptured posteriorly into the left pleural cavity I think you can see in the picture how large the rupture was and that it is no wonder that death occurred so suddenly It is worth nothing that the aneurysm of the ascending aorta and of the arch produced *physical signs*, while the larger aneurysm of the upper descending aorta did not cause physical signs but first made itself felt by pain in the back, and thus produced *symptoms*

THE DISCUSSION

The history of our present knowledge of thoracic aneurysm is a delightful one to delve into because it brings one among such fine company I shall attempt only to recall to your memories those pieces of work which seem to me to be of prime historic importance No two people could possibly pick out the same group of papers as being best suited to this purpose, for the choice is an arbitrary one and largely a matter of individual opinion I find myself, for example, admittedly partial to the medical accomplishments of the soldier-surgeons, of what Sir William Osler and Sir William Broadbent have contributed, and of the part played by Harvard men in this particular field of medical investigation

The story of aneurysm begins most picturesquely, with Ambroise Paré (1510–1590), a rustic barber's apprentice who became an army surgeon and finally the greatest surgeon of his time For it was he, by describing the case of "a man named Belanger, a master tailor living on the Pont Saint Michel near the sign of the Cock," who first drew attention to the interrelationship of syphilis and aneurysm You can read of this case in Malgaigne's "Oeuvres Complete d'Ambroise Paré,"* published in 1840, or perhaps, more easily, in one of the English translations The most

* The first edition of Paré's complete works was published in French in 1575 The second edition appeared in 1579 The first translation of the book from French to Latin was published in 1582—and our two copies contain the book-plates of James Jackson and of the first John C Warren The first English translation was made from the Latin edition and was published in 1634, being republished in 1649 So popular were Paré's works and considered of such importance that they were translated into German in 1601 and into Dutch in 1655 Anyone sincerely interested in Paré and his ideas should read the earliest possible French edition of his works, for translation from French into Latin and thence to English has proved, at least, a decolorizing process

venerable one which we have in the Harvard Medical School Library is the second edition, published in 1649 Here is what is written

"The *Aneurismaes* which happen in the internall parts are incurable Such as frequently happen to those who have often had the unction and sweat for the cure of the French disease because the blood being so attenuated and heated therewith that it cannot be contained in the receptacles of the Artery it distends it to that largness as to hold a mans Fist, Which I have observed in the dead body of a certain Taylor, who by an *Aneurisma* of the Arterious vein suddenly whilst he was playing at Tennis fell down dead, the vessel being broken his body being opened I found a great quantity of blood powred forth into the capacity of the Chest, but the body of the Artery was dilated to that largness I formerly mentioned and the inner coat thereof was bony For which cause within a while after I shewed it to the great admiration of the beholders in the Physitians School whilst I publiquely dissected a body there, the whilst he lived said he felt a beating and a great heat over all his body by the force of the pulsation of all of the Arteries, by occasion whereof he often swounded The cause of such a bony constitution of the Arteries by *Aneurismaes* is, for that the hot and fervid blood first dilates the Coats of an Artery, then breaks them, which when it happens, it then borrows from the neighbouring bodies a fit matter to restore the loosed continuity thereof"

The next paper on the cause of aneurysm which you should remember was written by another soldier, Francis H Welch,[1] in 1875, and was entitled "On Aortic Aneurysm in the Army, and the Conditions Associated with it" Osler says that this paper remains the most important communication on the subject in English, and I am glad to see that recently Dr E P Carter of Johns Hopkins and his colleague Dr B M Baker, Jr, have reawakened interest in its significance Here we find for the first time a very clear description of the macroscopical and microscopical appearance of syphilitic aortitis, and the view expressed "That in the adoption of preventive measures against

aneurysm, the attention must be primarily directed against the cause of the aortic disease, notably the suppression of syphilis, and secondarily, against the conditions of dress, etc, which assist in its development"

The third paper that one should know, by sight anyway, is the one by Schaudinn[2] and Hoffmann, appearing in 1905, and called "Vorlaufiger Bericht uber das Vorkommen von Spirochaeten in Syphilitischen Krankheitsprodukten und bei Papillomen" This paper described the results of the careful study of scrapings from syphilitic material in which were constantly found a pale-looking spirochaetal organism This organism had a peculiar morphological appearance, different in character from the darker looking spirochaetae that might be found in other conditions While no suggestion was made that such a "pale" spirochaeta was the cause of syphilis, yet the authors stated that it was not found in any of the other venereal lesions This report inevitably stimulated a great deal of work Presently confirmatory and experimental data were produced to show that the cause of syphilis had been discovered and that the Spirochaeta pallida was the etiologic agent The next step was in the description, by Levaditi, of a method for the proper staining of the Spirochaeta pallida in tissues—a method which was soon to become of great importance in connection with the study of aneurysm

In the early part of the century, the immunologists were hard at work and much effort was being spent on complement-fixation tests for the diagnosis of various infections Hence in 1906, immediate interest was aroused by a paper in the Deutsche medicinische Wochenschrift by Wassermann,[3] Neisser, and Bruck entitled "Eine serodiagnostische Reaktion bei Syphilis" These authors claimed to have found a serologic method for the diagnosis of syphilis and their claims were soon confirmed by other workers all over the world This paper, therefore, is the cornerstone on which has been built the most important single laboratory test available for the diagnosis of thoracic aneurysm

In such fashion, the relationship between syphilis and aneurysm was worked out, first by the process of direct observation and clinical-pathologic correlation, next by discovering the cause

of the primary disease, and then by finding a reliable but simple laboratory test through which was made possible the recognition of latent syphilis The final touch to this structure was added in 1909, by J H Wright[4] and Oscar Richardson in the pathologic laboratory of the Massachusetts General Hospital Their short paper "Treponemata (Spirochaetae) in Syphilitic Aortitis Five Cases, one with Aneurysm," is a model of scientific medical literature. It gives credit where credit is due, and describes clearly, succinctly, and without exaggeration, some most important facts

Fig 163 —Spirochaetae in wall of an aortic aneurysm (From Wright and Richardson)

Wright and Richardson studied histologically aortas from cases of syphilitic aortitis and aneurysm, staining the material by Levaditi's method. "The finding of the treponemata in an area of primary necrosis in the media as well as in association with the necrosis in the fibrous tissue seems to justify the feeling that the micro-organisms are to be regarded as the cause of the whole process, although the possibility that they are merely secondary invaders cannot be denied " That syphilis is the cause of the whole process is now generally admitted

Naturally during the years from 1600 to the present a great deal of clinical knowledge in regard to aneurysm developed

Case after case was reported, series of cases were worked up in various ways, usual and unusual physical signs were described, and each successive generation of students was made familiar with the bizarre manner in which thoracic aneurysm may make itself felt, may grow and may terminate Students in the seventies were referred for their reading to the monographs of Crisp (1846), Rokitansky (1850) or Broca (1856) For myself, in these times, I confess to an ever-increasing delight in reading and rereading the chapter on Aneurysm "by Prof W Osler, M D, F R S," which appeared in the 1910 edition of the System of Medicine edited by Sir Clifford Allbutt This differs but little from the chapter on Aneurism which the same author wrote for Osler's Modern Medicine in 1908, the chief difference being that in the English system "aneurysm" is spelled, punctiliously, with a "y" Another of my favorites is the chapter on "Aneurysm of the Arch of the Aorta" in Sir William Broadbent's book on "Heart Disease," a medical classic that everyone should know Add to these, interesting articles as they have come along in current periodicals from time to time, and one has an adequate library with which to study his cases

Dr Linn J Boyd,[5] working in Ann Arbor in 1924, did those of us with a statistical turn of mind a great service by "A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta" The figures assembled in this paper are not difficult to remember and give at a glance a bird's eye view of the subject which is worth having

Thoracic aneurysm is not a rare disease, and is about five times more common in men than women, it may be seen at any age but most often in individuals around forty Sudden violent exertion may precipitate a latent aneurysm, although the association of syphilis, alcohol, and hard work in the same individual is more important than occupation itself

Thoracic aneurysms occur most frequently in the ascending aorta (48 per cent), next most commonly in the arch of the aorta (32 per cent), more rarely in the upper descending aorta (15 per cent) and quite rarely in the lower descending aorta (5 per cent) Not infrequently aneurysms are multiple

Shortness of breath, pain in the chest and cough are the three common symptoms of thoracic aneurysm

Patients with thoracic aneurysm do not often live long after the disease is recognized Occasional cases are reported, however, which have lived comfortably with the disease from ten to thirty years after its discovery About 80 per cent of the cases die within two years after the diagnosis is established

Half the cases die of rupture, and aneurysms in different situations tend to rupture more or less according to rule The common places of election for rupture are shown in the following table

	Ascending aorta per 100 cases.	Arch of aorta per 100 cases	Upper descending aorta per 100 cases.	Lower descending aorta per 100 cases.
Pericardium	57	13		2
Left pleura	2	13	30	46
Esophagus	2	13	19	14
Right pleura	3	10	10	12
Left bronchus		14	23	4
Trachea	1	16	5	
Externally	5	4		
Pulmonary artery	10	1		
Superior vena cava	8	2		
Left lung		3	5	10

Bearing these figures in mind, it is most important in the study of any individual case to remember the position and chief anatomical relations of the aorta Most of the symptoms and physical signs of aneurysm are directly dependent on pressure effects on the structures adjacent to the dilated portion of the vessel.

Part of the aorta lies free in the pericardial cavity for a short distance from its origin, aneurysms of this intrapericardial portion, more especially of one of the sinuses of Valsalva, are

liable to rupture and to cause sudden death before any physical signs or symptoms arise Above this point, the ascending portion grows forward, is near the surface of the chest and accessible to physical examination It has no attachment to surrounding structures, and enjoys considerable freedom of movement Aneurysm here often attains to considerable size

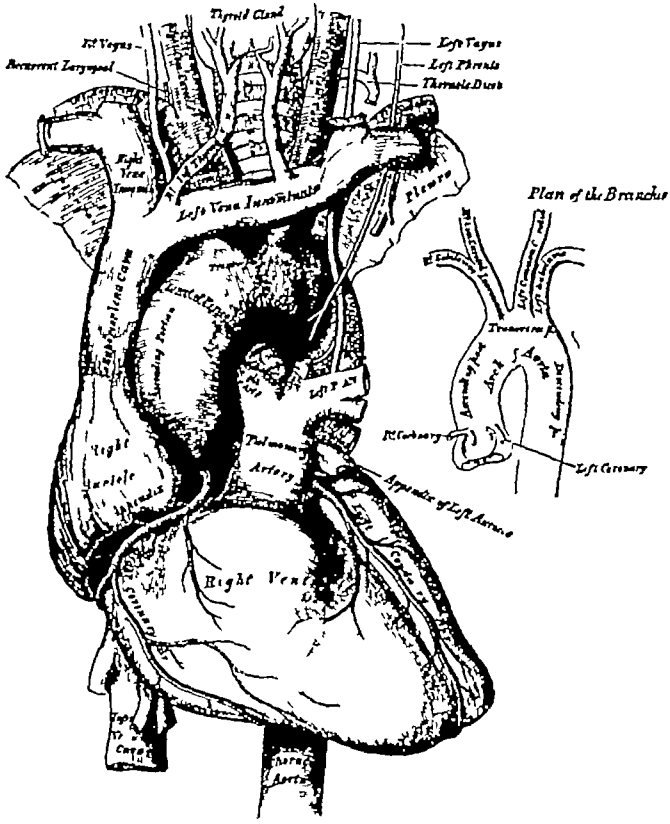

Fig 164 —The aorta and its relations (From Gray's Anatomy)

before it begins to give rise to any symptoms from pressure on surrounding organs, so that the first indication of its presence may be a pulsating tumor visible on the chest wall to the right of the sternum

The transverse portion of the arch, on the contrary, is deeply placed, points backward and to the left is more firmly fixed in

position, and is in such close relation to various important structures, that an out-pocketing from its surface cannot elude or be eluded by the surrounding organs Hence aneurysm of this portion of the aorta usually gives rise to symptoms from pressure on adjacent structures before it attains any great size Of these a brassy cough, a tracheal tug and difficulty of deglutition may be the first indications

The descending aorta is deeply seated The only important structures in immediate relation are the esophagus and thoracic duct Frequently the only symptom complained of from aneurysms here is pain in the back there may be no other physical signs or symptoms present

These facts led Sir William Broadbent to divide thoracic aneurysm into his two famous classes, *Aneurysm of Physical Signs* and *Aneurysm of Symptoms* The former term applies to aneurysms of the ascending aorta and first part of the arch, the latter to aneurysms of the transverse and descending portions of the aorta.

I shall not waste your time with a recitation of the common physical signs of aneurysm for with these, I am sure, you are all familiar Remember, however, what Sir William Osler has said "There is no disease more conducive to clinical humility than aneurysm of the aorta "

Always be on the lookout for it in anyone complaining of pain in the chest, dyspnea or cough Osler's command, "Strip to the buff," is the rule If the shirt and undershirt are tucked up to save time, the all important area above the level of the second rib may be covered Turn the patient and examine the back, particularly the interscapular areas If this is not done as a routine, the chances are it will be forgotten and perhaps the diagnosis may be missed altogether To test for tracheal tug, carry out the procedure as described originally by Surgeon-Major Oliver [6] "Place the patient in the erect position, and direct him to close his mouth and elevate his chin to almost the full extent, then grasp the cricoid cartilage between the finger and thumb, and use gentle upward pressure on it, when, if dilatation or aneurysm exist, the pulsation of the aorta will be

distinctly felt transmitted through the trachea to the hand The act of examination will increase laryngeal distress should this accompany the disease" Bear in mind the importance of the aneurysmal second sound It is difficult to describe, for it may be low-pitched and musical or loud and ringing If it is accompanied by a palpable diastolic shock, however, it is a very helpful sign Remember that the heart is not enlarged unless there is an accompanying aortic insufficiency The apex beat may be displaced considerably and be found below or outside its normal position but this should not be mistaken for hypertrophy

The picture produced by rupture may be very interesting and some of its characteristics may be worth mentioning When an aneurysm ruptures into the pericardium death is sudden It is usually an unexpected necropsy finding When an aneurysm ruptures into the pleural cavity, it also usually proves fatal within a short period of time When an aneurysm ruptures into the esophagus, the process is apt to be one of gradual erosion with first dysphagia, then local necrosis and gangrene, often leading to the suspicion of cancer of the esophagus instead of the correct diagnosis When an aneurysm ruptures into the bronchus or trachea there may be a sudden fatal hemorrhage But more frequently a chronic tracheitis occurs first and bloody sputa may appear and disappear over long periods of time, or there may develop bronchiectasis and infection with a very confusing picture When an aneurysm ruptures externally it at first "weeps" and finally bursts with sudden death When an aneurysm ruptures into the pulmonary artery, the immediate symptom is sudden pain in the chest, dyspnea, and perhaps cough with a little blood-stained sputum A continuous roaring murmur develops, and this may be accompanied by a thrill When an aneurysm ruptures into the superior vena cava the immediate symptoms are severe dyspnea, cyanosis, edema of neck and face and the development of distended veins on the front of the chest from collateral circulation established between the internal mammary and the intercostal and superficial epigastric veins When an aneurysm ruptures into the lung,

slight and recurring hemoptysis may occur and there may de velop signs of atelectasis

I hope that during this discussion you have kept in mind the case which I have reported and agree with me in finding it of more than usual interest. For this patient had as you may recall, clinically, as well as radiologically and pathologically what amounted to two lesions an aneurysm of signs and an aneurysm of symptoms The aneurysm of signs produced an increased retrosternal dulness, a heaving expansile thrust to the upper chest, and a ringing aneurysmal second sound Originating in the ascending aorta, it was able to grow forward without producing any particular pressure symptoms and therefore, did not cause discomfort. The aneurysm of symptoms, on the other hand, was in the descending aorta and produced pain in the back It was not near enough to the surface to produce any signs Death, quite properly, was caused by rupture of this aneurysm into the left pleural cavity, as this is the manner in which nearly half of such cases end Had the aneurysm of signs ruptured, it would have been more likely to have broken into the pericardium, the pulmonary artery, or the superior vena cava

A careful clinician who takes a good history and knows physical diagnosis should be able to make the diagnosis of aneurysm and to locate the lesion in most cases with a fair degree of accuracy There are two adjuvants to clinical knowledge, however, which are very useful These are the Wassermann reaction and the *x* ray

The Wassermann reaction in cases of aneurysm is likely to be positive In the latest figures that I have seen, Moore,[7] Danglade, and Reisinger of Johns Hopkins found it positive in 50 out of 52 cases (98 per cent) I have looked up the records of a group of 57 of the Peter Bent Brigham Hospital cases and here the test was positive in 50 (88 per cent) This means that in the doubtful case in which the diagnosis rests between aneurysm and some other intrathoracic lesion, a negative Wassermann reaction points against the diagnosis of aneurysm while a positive reaction is a bit of evidence in its favor

I am sure that everyone nowadays agrees as to the diagnostic

value of the x-ray and fluoroscope Certain aneurysms are detected by this method of study which could not possibly be recognized by any other means

The treatment of aneurysm is only fairly satisfactory but is making slow but sure progress Vigorous antiluetic medication unquestionably is of some value in most cases I think that several courses of mercury and of iodide combined with three of neoarsphenamine were of help to the case I have described The symptom of pain disappeared very quickly, the patient gained 15 pounds in weight, little by little, and was able to lead an active life for several years after the cause of his troubles was recognized During this period, however, the aneurysm grew in size, as the x-ray demonstrated, and the disease ended in typical fashion The patient was an elderly person, and on this account, one might have predicted a relatively benign course for the illness The results of treatment, therefore, in this case, are difficult to evaluate

The results of treatment which have been reported by Moore, Danglade, and Reisinger are more convincing Of 25 patients with aortic aneurysm who received but little treatment, the average duration of life from the onset of symptoms to death was only nineteen months But in 15 cases which were adequately treated, there were many fewer deaths and the average duration of life was seventy-five months They used for medication, bismuth, iodide, bismuth arsphenamine sulphate (bismarsen), and small doses of neoarsphenamine in selected cases They emphasize the need of continuous and prolonged treatment and paid no attention to the response of the Wassermann reaction since Wassermann fastness is the rule I think that their therapeutic suggestions are well worth following, certainly their results appear impressive

Surgery, too, rarely may have something to offer So long ago as 1864, Moore[8] and Murcheson reported "On a new method for procuring the Consolidation of Fibrin in certain incurable aneurysms," in which they described a case which was wired, and ever since sporadic efforts have been made to improve this method On the whole, procedures of this sort have not been

strikingly successful Recently a new plan of surgical attack has been suggested Dr J C White[9] has reported 3 cases of aneurysm at the Massachusetts General Hospital in which the very distressing symptom of pain unrelievable by antiluetic remedies was dramatically helped by paravertebral injections of procaine or alcohol This operation which is relatively simple may be well worth while to keep in mind

I began this clinic with a case report In discussion, I have tried to show on what foundation our knowledge of thoracic aneurysm has been built, what a serious affliction is this disorder and along what lines its treatment is now best pursued I end with a look to the future Aneurysm is due to an infection that can be prevented Perhaps, as time goes on, as Osler hoped, perhaps at the very outset, at the portal of entry the disease may be jugulated.

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CLINIC OF DR HERRMAN L BLUMGART

MEDICAL SERVICE, BETH ISRAEL HOSPITAL

THE CLINICAL SYNDROME OF SUBACUTE BACTERIAL ENDOCARDITIS INVOLVING THE RIGHT CHAMBERS OF THE HEART

SUBACUTE bacterial endocarditis has an importance somewhat out of proportion to its frequency, partly on account of its great gravity, and partly because of the difficulties which frequently attend the diagnosis In cardiac patients with fever, the presence of clubbed fingers, splenic enlargement, hematuria, petechial hemorrhages and other evidence of embolic phenomena readily suggests the diagnosis of subacute bacterial endocarditis, the isolation of the invading organism by blood cultures conclusively establishes the diagnosis The importance of the search for peripheral embolism and blood stream infection cannot be overestimated as the diagnosis of the disease turns largely on their discovery It is not sufficiently recognized, however, that when the pathologic process is confined to the right chambers of the heart the peripheral embolic phenomena and peripheral blood stream infection may be absent. The diagnosis must then be made on the basis of a different but nevertheless characteristic syndrome of symptoms and signs The purpose of this clinic is to present this characteristic syndrome together with its explanation based on the observed underlying pathology

Case I.—B I H 12 808 The first patient to be presented is a nineteen year old single stenographer who was admitted to the Beth Israel Hospital on January 13 1932 complaining of persistent cough chills and fever The family and social histories are irrelevant. She has not had rheumatic fever chorea, scarlet fever diphtheria pleurisy malaria or influenza. For the past six or seven years she has had two or three attacks of acute tonsillitis each year Since the age of two years she has been known to have a heart

murmur that was considered of no consequence She has always felt perfectly well, has been a vigorous worker, and has been able to indulge in the usual activities of girls of her own age Her weight was 118 pounds six months ago, her weight at the time of entry to this hospital, five weeks ago, was 113 pounds, the present weight is 123 pounds

The present illness began four and a half weeks before entrance to this hospital when, without evident cause, she experienced chills lasting one half hour She felt well the following day, returned to work, but was forced to bed early in the evening by a recurrence of chills During the following week, or until three weeks before entry, she suffered malaise, weakness, two or three chills daily, accompanied by fever of 101 to 102 F , and a sharp "pulling" pain in the left flank which radiated to the back The pain varied in intensity but never disappeared entirely Coincident with this pain, the patient experienced frequency and burning micturition but no evident hematuria or polyuria She was informed by her physician that she was suffering from pyelitis

One week before entry a sharp "pulling" pain appeared in the right flank similar to that previously present in the left flank The pain was persistent and was aggravated somewhat by motion and particularly by micturition There was no pain in the right or left upper quadrants of the abdomen At about this same time, the patient began to be troubled by a persistent nonproductive cough and pain in the left chest and axilla which was aggravated by deep inspiration Because of the persistent fever, malaise, burning micturition, and cough during the week before entry, the patient was referred to the hospital

Physical examination at the time of admission showed a fairly well developed young girl lying flat in bed, apparently quite comfortable There were no conjunctival or retinal hemorrhages and no petechiae Over the left midback at the angle of the scapula and corresponding to the area where the patient experienced pain, dulness, bronchial breathing, and increased transmission of whispered and spoken voice were evident Similar physical signs were present over the right back, particularly at the base. Examination of the heart showed dimensions well within the limits of normal The ventricular rate was 96 per minute, the rhythm regular, and the sounds not particularly hyperactive in quality Over the pulmonic area a sharply localized soft systolic murmur and a much fainter diastolic murmur were audible No thrills were palpable The blood pressure was 118 mm Hg systolic, 68 mm Hg diastolic The radial pulses were equal and synchronous and there were no peripheral signs of aortic insufficiency The abdomen was soft and nontender The spleen could not be felt and no enlargement was evident by percussion There was no costovertebral tenderness There was no peripheral adenopathy The fingers and toes showed no tenderness or clubbing The superficial and deep reflexes were normal Examination of the blood showed 4,000,000 red blood cells per cubic millimeter, the hemoglobin 70 per cent by Tallquist, the white blood cell count 10,000 per cubic millimeter, of which 73 per cent were polymorphonuclear neutrophils, 22 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophils Examination of the blood smear showed no evidences of anemia and no malarial organisms Platelets were normal Examination of an uncatheterized

specimen of urine showed completely normal findings The stools were normal The Wassermann Kahn and Hinton tests were negative The Widal reaction for Bacillus typhosus and Paratyphosus A and B was negative. Agglutination tests for undulant fever were likewise negative. Cultures of the peripheral blood showed no growth of organisms Electrocardiographic tracings showed completely normal curves. There was no right or left axis deviation

Stereoroentgenographical examination of the chest by Dr Samuel A Robins showed patches of consolidation in both lower lung fields. Both sides of the diaphragm were clearly outlined the right and left costophrenic angles were hazy The findings were in harmony with the physical signs and indicated a pneumonic process in both lower lobes. Roentgenograms of the kidneys showed both kidney outlines visible and normal in contour size and position

Diagnosis—The findings in this patient pointed to two definite pathologic processes one affecting the heart the other the lungs. The negative history of rheumatic infection and the absence of clinical signs of mitral or aortic valvular heart disease practically ruled out the possibility of chronic rheumatic involvement of the heart the most frequent cause of heart disease in subjects the age of our patient The presence of a harsh systolic and a softer less prominent early diastolic murmur in the pulmonic area and the history of pathologic murmurs heard since childhood supported the diagnosis of congenital heart disease possibly patent ductus arteriosus or interventricular septum defect with or without pulmonary stenosis.

The history of burning micturition and pain in both flanks with a septic temperature suggested the possibility of pyelitis but the negative urine findings the normal kidney outlines with absence of costovertebral tenderness on palpation and percussion failed to support a diagnosis of renal pathology The physical signs in the chest and *x* ray findings pointed definitely to bronchopneumonic involvement of the lungs. It was difficult however to believe that this condition was the primary cause of the patient s complaints. Bronchopneumonia in young individuals is usually a self limited disease whereas, in this patient cough and fever had continued for several weeks without signs of abatement The patient felt surprisingly well moreover and the absence of cyanosis and dyspnea were not in accord with a diagnosis of primary bronchopneumonia. The findings given during the presentation of the patient ruled out such possibilities as malaria miliary tuberculosis, typhoid or paratyphoid fever or undulant fever

The diagnosis of acute or subacute bacterial endocarditis could not be established The evidence on which this diagnosis usually rests was absent There were no signs of peripheral embolic phenomena, no clubbing of the fingers, variations in the cardiac murmurs enlargement of the spleen evidence of acute glomerular or focal nephritis and the blood cultures were persistently negative. The continued presence of septic temperature with a leukocytosis persistently near the upper limits of normal suggested however by the process of exclusion that we were dealing with an infection caused by an organism of relatively low virulence. Our inability to localize the infection elsewhere in the body together with the evidence of pathologic processes in the right chambers of the heart and in the lungs suggested that the primary

site of the infectious process was probably in the right chambers of the heart and that the pulmonary pathology was due to emboli thrown out into the lung fields These findings were consistent with a diagnosis of subacute bacterial endocarditis superimposed on a congenital heart defect with secondary multiple infarcts in the lung, and so a presumptive diagnosis of these conditions was made It was decided, however, not to inform the patient's relatives until the diagnosis could be established with absolute assurance

Course of Illness —The patient was placed on a high caloric diet because of the prolonged fever and she gained 10 pounds in weight She felt perfectly comfortable Eleven urine examinations showed no abnormal findings and seventeen white blood examinations were not remarkable except for three counts of 13,200 to 15,000 cells per cubic millimeter Repeated examination of the chest showed persistence of the process in the lung with marked fluctuations in its extent Six blood cultures were made on various occasions during the rise in temperature after chills Two cultures made subsequently were reported as positive for nonhemolytic streptococci At no time have petechiae, peripheral embolic phenomena, enlargement of the spleen or clubbing of the fingers been present

Conclusive proof of the explanation of the clinical syndrome just presented would be dependent on postmortem verification Before discussing the significance of some of the phenomena shown by this patient, it will be of interest, therefore, to review the clinical and postmortem findings of another case

Case II —B I H 469 The patient was a thirteen year old school girl who entered the hospital complaining of malaise, loss of weight, and pain in the upper and lower extremities, eight months in duration The family history was negative According to the patient's past history, the diagnosis of congenital heart disease had been made when she was two and a half years of age She had had chickenpox, diphtheria, measles, mumps, whooping cough, influenza, and had had several attacks of tonsillitis There was no history of acute rheumatic fever or chorea

Present Illness —The patient had felt perfectly well until eight months previous to admission when, without evident cause, she experienced the gradual onset of malaise, anorexia, and fever, the latter being present in the evening and night but disappearing by morning From time to time she experienced pains referable to various parts of the abdomen, but somewhat more frequently to the left upper quadrant She also experienced occasional pains in both legs with tingling sensations in the thighs and in the toes Approximately seven months previous to entrance into the hospital the patient noticed that the urine was at times reddish, and that she was troubled by frequency During the month previous to her coming to the hospital she developed an irritative nonproductive cough, and was troubled by pain in the chest aggravated by deep inspiration Because of the increased severity of the cough and other symptoms, the patient entered the hospital for diagnosis and treatment

Physical examination showed a fairly well-developed and nourished girl with greenish yellow color of the skin She was mentally clear and coopera tive. Examination of the lungs showed dulness at the right base but the breath sounds were normal The heart according to palpation and per cussion was slightly enlarged The rhythm was regular the rate 124 per minute. A loud harsh rather high pitched murmur was heard everywhere over the precordium but especially over the sternum at the level of the third rib A short early diastolic murmur was audible and systolic and diastolic thrills were palpable over this area The second pulmonic sound was markedly

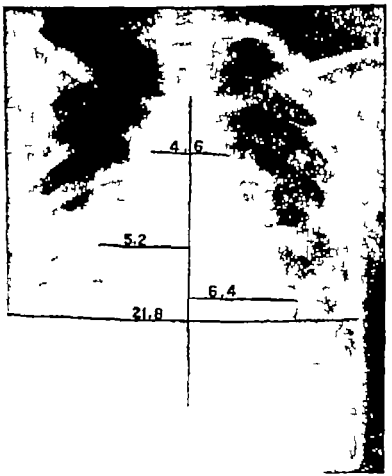

Fig 163 —Roentgenogram of heart and lungs showing coarse mottling in both lung fields due to septic infarcts.

accentuated The brachial blood pressure was 114 mm Hg systolic 72 mm Hg diastolic, and was equal in both arms The radial pulses were equal and synchronous and there were no peripheral signs of aortic insufficiency The spleen was slightly enlarged by palpation and percussion No abdominal tenderness was elicited by palpation No cutaneous or conjunctival petechial hemorrhages could be seen There was no clubbing of the fingers or toes.

Examination of the blood showed 4 000 000 red blood cells per cubic millimeter the hemoglobin 70 per cent The white blood count varied from 14 000 to 17 000 per cubic millimeter of which approximately 75 per cent were polymorphonuclear neutrophils 20 per cent lymphocytes and 5 per

cent monocytes Platelets were normal The urine contained the slightes possible trace to a trace of albumin, many red blood cells, and occasiona brown granular and hyaline casts The nonprotein nitrogen concentratio in the blood was normal Roentgenographical examination of the ches showed increased width and density of the hilus shadows and the presence o coarse mottling in both lower lung fields (Fig 165) The diaphragm wa sharply defined and the costophrenic angles were clear The heart was slightl

Fig 166.—Heart of Case II The valves and endocardium of the left ventricle are free of vegetations The vegetations on the mural endocardium of the right auricle and ventricle, and the vegetations on the tricuspid valve are shown The lower probe is shown passing through the interventricular septum defect The upper probe is shown passing through the potentially patent foramen ovale

enlarged in the transverse diameter The electrocardiographic tracings were normal Repeated cultures of the peripheral blood were negative

Diagnosis.—The diagnoses of congenital heart disease, subacute bacterial endocarditis, multiple septic pulmonary infarcts, and acute glomerulonephritis were made.

Course of Illness.—The clinical course was rapidly downward Petechial spots appeared in the fundi of the eyes and also over the abdomen The

signs of consolidation in the lung were heard over more extensive areas numerous crepitant and moderately coarse râles were heard everywhere over both lung fields the secondary anemia of the blood became more pronounced, the respiratory rate became more rapid and more labored pulmonary edema appeared and the patient died

Fig 167.—Section of lung (magnification × 10) showing several miliary infarcts of the lung Thrombosed arteries indicated by arrows.

Postmortem Examination.—I am deeply indebted to Dr Monroe J Schlesinger Pathologist to the Beth Israel Hospital for his careful notes and study of this case The heart was moderately enlarged The pericardium was normal The ductus arteriosus was represented by a small fibrous cord which was not patent. The tricuspid valvular ring was somewhat enlarged and the orifice almost completely filled with irregular soft friable yellowish white masses of vegetations (Fig 166) The valvular leaflets had been

almost entirely destroyed by the vegetations, which extended down over the mural endocardium of the upper half of the right ventricle It is frequently impossible to be certain whether the tricuspid valve has been the site of a congenital lesion or whether the condition of the valve is the result of an acquired infective lesion [10] The appearance of the tricuspid valvular ring in this patient indicates that the tricuspid stenosis was not a congenital defect but was due to occlusion of the orifice by the redundant masses of vegetations The endocardium of the right auricle was not involved Microscopical examination of crushed fragments of the vegetations disclosed enormous numbers of short chained streptococci consistent in appearance with streptococcus viridans The pulmonary valve was entirely normal The left chambers of the heart showed no evidence of endocarditis and both the mitral and aortic valves were normal A sinus tract, 8 mm in diameter and 3 mm in length, was present in the membranous part of the interventricular septum just below the mitral valve The tract was obviously infected, the lumen being lined with soft grayish material The orifice of the tract in the left ventricle was clean and devoid of vegetations indicating that the flow of blood during life had been entirely from the left to the right ventricle. A probe passed through the tract from the left ventricle emerged in the right ventricle in the midst of the large vegetative masses at the base of the tricuspid valve A slitlike patent foramen ovale, well protected by flaps in either auricle, was also present

The lungs were bloody and many firm nodular areas were palpable. On section some of these areas showed necrotic soft centers, a result, presumably, of septic emboli The larger pulmonary arteries and veins showed no evidence of thromboses or emboli but, microscopically, infected emboli were readily found, especially in conjunction with the septic infarcts (Fig 167) The spleen was enlarged and the capsule irregularly thickened The kidneys showed a typical picture of acute and chronic glomerulonephritis, including thrombosis of many glomeruli and all stages up to complete fibrosis The tubules contained many hyaline and cellular casts and showed secondary degenerative changes The pathologic diagnoses were congenital heart disease with interventricular septum defect and patent foramen ovale, subacute bacterial endocarditis of the tricuspid valve, the latter showing stenosis and insufficiency, septic infarction of the lungs, acute and chronic glomerulonephritis, hypertrophy and dilatation of the heart, chronic fibrous splenitis, and chronic passive congestion of the liver and spleen

DISCUSSION

The case just reviewed illustrates a later stage of the clinical progress of the same condition seen in the first patient On the basis of these 2 cases the life history of the disease can be reconstructed and the clinical phenomena can be more readily understood The syndrome of subacute bacterial endocarditis involving the right chambers of the heart differs from the more usual

syndrome of involvement of the left chambers of the heart in that the classical signs of splenic, renal, and cerebral infarcts and other evidence of peripheral emboli may be absent In their place one finds irregular manifestations of protracted pulmonary infection This infection is due to the continual accession of multiple small emboli in the fine capillary mesh work of the lungs In a patient with congenital heart disease and the signs of pulmonary infection the relationship between these two becomes more readily established on the basis of these observations In brief, the syndrome of subacute bacterial endocarditis affecting the right chambers of the heart consists in (1) the presence of a cardiac lesion involving the right chambers of the heart, (2) generalized evidences of infection, *i e*, fever, tachycardia, leukocytosis, etc., (3) instead of evidences of peripheral emboli in the greater circulation, the symptoms and signs of protracted atypical pulmonary infection due to multiple septic infarcts Only in the far advanced stages of the disease when necrosis of the septic pulmonary infarcts occurs may organisms be released from the lungs into the greater circulation The more usual features of the disease may then appear and positive blood cultures may be obtained. If the sequence of events just described is borne in mind, however, the diagnosis of subacute bacterial endocarditis frequently can be made relatively early and many months of indecision and suspense may be obviated

The importance of the above considerations is shown by one of the cases observed by Sir Thomas Horder some twenty-eight years ago [3] The characteristic features of the syndrome are so vividly described that it will be of interest to quote the case history in full

A boy age seven years was admitted under the care of Dr Gee, in July 1904 on account of short breath and cough Bronchitis was present There was no cyanosis but the fingers were somewhat clubbed Quotidian intermittent fever lasting for some three months, suggested infection of a congenitally defective heart but two blood cultures yielded no growth of micro-organisms Eventually the fever subsided though it did not completely disappear and the boy was sent to a convalescent home Three weeks later he returned to hospital under the care of Dr Herringham again suffering

from bronchitis A very loud and prolonged systolic murmur was heard all over the chest and also at the back, its maximum intensity was over the pulmonary area and down the left border of the sternum Six weeks later signs of kidney disease appeared—hematuria, albuminuria, scanty urine, and edema There was practically no fever The edema increased and the boy eventually died, three months after his second admission and eight months after the onset of his illness *Postmortem* Both right and left chambers of the heart were much dilated, as also were the mitral and tricuspid valves Both ventricles were somewhat hypertrophied The aortic, mitral, and tricuspid valve cusps were all natural The pulmonary valve cusps showed numerous warty vegetations but no evidence of congenital disease. These vegetations spread a little way along the wall of the pulmonary artery In the conus, just below the pulmonary valve, was a firm fibrous band, which had probably caused some pulmonary stenosis The septum ventriculorum was patent above, by a hole as large as a sixpence. The heart's blood, the vegetations, and the spleen were sterile after cultivation, but the vegetations and heart-wall showed numerous masses of minute gram-negative bacilli in section, probably influenza bacilli "

The localization of the pathologic process to the right chambers of the heart, the presence of fever, etc , the sterile blood cultures during life together with the prominent pulmonary features and the complete absence of peripheral embolic phenomena, except for hematuria appearing only six weeks before death, exemplify strikingly the cardinal features of the syndrome Another case illustrating many of the features of this syndrome has been described recently by White and Boyes [12] All these cases showed interventricular septal defects but the syndrome may, of course, appear in any case which shows right-sided subacute bacterial endocarditis regardless of whether the underlying lesion is or is not a congenital defect It is of interest to note that, in the two instances in which Libman[5] observed embolic vegetations in the pulmonary vessels, right-sided lesions were present

The presence of hematuria in Case II and also in Horder's case suggests the late appearance of embolic glomerulonephritis as described by Loehlein[6] and considered characteristic by Baehr and Lande [1] It should be observed, however, that hematuria and petechiae are considered by some to be an expression of a hemorrhagic tendency in this disease rather than related to embolism [3, 11] The completeness with which the lungs

evidently are able to hold back the numerous organisms delivered in the infected pulmonary blood is remarkable and explains why the more usual clinical features of subacute bacterial endocarditis upon which reliance is so strongly placed are lacking in this form of the disease This sievelike quality of the lungs which enables the withdrawal of bacteria from the active circulation is also shown by certain cases of myelogenous leukemia in which cough is a prominent symptom and in which pathologic section reveals many of the pulmonary capillaries occluded by these large myeloid cells [7]

Patients with lesions in the left chambers of the heart may also show cough and other pulmonary signs This may be due to pulmonary congestion for we encounter a similar cough in certain phases of mitral stenosis Irritation of enlarged tracheobronchial nodes[5] and emboli in the bronchial arteries[4] have also been suggested as possible causes of cough in subacute bacterial endocarditis, but in any case, the appearance of such features along with the other evidences of left sided lesions should present no difficulties in diagnosis Similarly, the other evidences of left-sided lesions will clarify the diagnosis in cases which are in the bacterial free stage with negative blood cultures

The fact that the pathologic processes were confined to the right chambers of the heart in these cases illustrates the well-known predilection of subacute bacterial endocarditis to develop on the site of previous endocardial injury [9 8] This tendency is so great that, as pointed out by Fulton and Levine, one can practically dismiss the diagnosis of subacute bacterial endocarditis in any doubtful case if no murmurs are present A similar infrequent association of auricular fibrillation and subacute bacterial endocarditis has been noted by Libman,[5] the presence of the former condition tending to rule out the diagnosis of the latter condition

The absence of cyanosis and clubbing of the fingers and toes in our patients is of particular interest since these two signs occur not only in subacute bacterial endocarditis but also in patients with congenital heart disease It is not sufficiently recognized, however, that the majority of patients with con

genital heart disease do not show cyanosis One of the main causes of cyanosis in patients with congenital heart disease is the presence of veno-arterial shunts The left ventricle of the second patient and possibly that of the first patient communicated freely with the right ventricle by means of an interventricular septal defect The complete absence of vegetations on the endocardium of the left ventricle, the absence of organisms in the peripheral blood and the clinical absence of cyanosis indicate that the higher pressures developed by the left ventricle caused blood to flow from the left ventricle to the right ventricle and that no significant flow of blood in the reverse direction occurred

These cases of subacute bacterial endocarditis engrafted on the site of a congenital defect illustrate the peril to which patients with such lesions are continually exposed, and the necessity of a guarded prognosis in spite of the fact that, in the absence of such infection, patients with congenital defects may live comfortably to advanced years and even surpass the average duration of human life

SUMMARY

In cardiac patients with fever, the presence of clubbed fingers, splenic enlargement, hematuria, petechial hemorrhages, and other evidence of embolic phenomena readily suggests the diagnosis of subacute bacterial endocarditis, the isolation of the invading organism by blood cultures conclusively establishes the diagnosis The importance of the search for peripheral embolism and blood stream infection cannot be overestimated as the diagnosis of the disease turns largely on their discovery It is not sufficiently recognized, however, that when the pathologic process is confined to the right chambers of the heart the peripheral embolic phenomena and peripheral blood stream infection may be absent The diagnosis must then be made on the basis of a different but nevertheless characteristic syndrome of symptoms and signs The syndrome of subacute bacterial endocarditis affecting the right chambers of the heart consists in (1) the presence of a cardiac lesion involving the right chambers of the heart, (2) generalized evidences of infection, *i e*,

fever, tachycardia, leukocytosis, etc., (3) instead of evidences of peripheral emboli in the greater circulation, the symptoms and signs of protracted atypical pulmonary infection due to multiple septic infarcts Only in the far advanced stages of the disease when necrosis of the septic pulmonary infarcts occurs may organisms be released from the lungs into the greater circulation The more usual features of the disease may then appear and positive blood cultures may be obtained If the sequence of events described is borne in mind, however, the diagnosis of subacute bacterial endocarditis frequently can be made relatively early and many months of indecision and suspense may be obviated

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CLINIC OF DRS HOWARD B SPRAGUE AND PAUL D WHITE

FROM THE CARDIAC CLINIC AND LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL

NITROGLYCERIN COLLAPSE—A POTENTIAL DANGER IN THERAPY REPORT OF THREE CASES

IT IS not uncommon for a patient who is first advised to try nitroglycerin for attacks of angina pectoris to express apprehension about the use of a drug with such an impressive name He is usually assured by his physician that the explosive effects are not to be feared and that the most disagreeable symptoms that he may have from its use are flushing of the face, or a thumping headache The more serious results of nitroglycerin absorption have been observed by us in 3 cases and make us believe that early warnings by Field, 1858,[2] and by Honert, 1867,[1] and the dubious opinion of some patients about a trial of this medicine should at least be kept in mind by the doctor who prescribes it A rather similar situation exists as regards toxic amblyopia from digitalis in that it was described by Withering early in the use of the drug but was forgotten and rediscovered several times in the next century

In a recently published article Prodger and Ayman[3] have reviewed the rather scanty literature on the subject and have reported 4 cases out of 110 tested with nitroglycerin showing profound collapse immediately after sublingual doses of 1/150 to 1/50 grain of the drug The blood pressure could not be determined in 2 cases and the pulse could not be felt Heart block was proved to be present by electrocardiogram in 1 case during the syncope and the progress of a cardiac infarction was unfavorably influenced in the other They refer to 2 patients mentioned by White[4] who had syncopal attacks after 1/100 grain of nitro

glycerin These 2 cases we wish to describe more fully as well as one other seen by one of us since, out of a total of 900 cases of angina pectoris, almost all of whom have used nitroglycerin

Case I —The patient was a man of fifty two who was seen October 30, 1924, at a time when he was having slight attacks of faintness and nausea associated with a respiratory infection These had come on when he was attempting to continue his legal work At that time nothing wrong with his heart was discovered on physical examination The blood pressure was 110 mm systolic and 80 mm diastolic He was not seen again until April 11, 1931 He then said that for the past two years he had had a little substernal oppression on exertion radiating toward the axilla His local doctor had discovered mild hypertension and a year before he was seen by us a diagnosis of angina pectoris had been made Four days before our consultation he began to have an increase in the severity and frequency of his attacks of pain He had been quite fatigued and had had an attack of grippe a few weeks before He had taken no medicine but carried nitroglycerin although he had never tried it Physical examination showed him to be in good general condition The blood pressure was 155 mm systolic and 95 mm diastolic The heart was regular at a rate of 72 The apex and left border of dulness of the heart were 8½ cm to the left of the midsternal line and in the midclavicular line The sounds were of fairly good quality and there were no murmurs There was no evidence of congestive failure Fluoroscopic examination showed the heart to be slightly enlarged with slight thickening and tortuosity of the aorta At the end of the examination, while his condition was being discussed, he had an attack of substernal oppression which was quite severe He put a tablet of nitroglycerin, grain 1/100, under his tongue and in a very short time he became faint and had profuse perspiration The pulse became very small and the heart sounds very faint and the rate slow He collapsed, became very gray and almost comatose, but gradually revived upon inhalation of aromatic spirits of ammonia and a drink of cold water He remained faint for fifteen or twenty minutes As the heart action improved and the faintness decreased, the pain returned He was admitted to the hospital where two ½-grain doses of morphine had to be given in the afternoon and evening to relieve the pain The blood pressure next day was 130 mm systolic and 90 mm diastolic. No change was noted in the examination of the heart at any time His temperature, however, rose to 102 F and the white count to 16,500

Electrocardiogram taken April 14th showed slight right axis deviation and inverted T waves in leads I and II, characteristic of coronary thrombosis A friction rub was audible over the precordium on April 16th The blood pressure on that day was 115 mm systolic and 75 mm diastolic At the time of his discharge from the hospital, May 14th, the electrocardiogram showed intraventricular block with inversion of the T wave in lead I The blood pressure had returned to 140 mm systolic and 90 mm diastolic but the heart had increased somewhat in size He has been improving since that time and when last seen October 22, 1932, was in a good state of health

Case II—The second patient was a man of sixty-eight who was seen shortly after the first patient namely on April 23 1931 He had always been well and active except that for a few years he had been somewhat dyspneic upon climbing stairs His father had died suddenly at the age of seventy On the day that the patient was first seen he had noted a little dyspnea after climbing the subway stairs and therefore he took a nitroglycerin tablet at the advice of a friend who used this drug himself He promptly fainted and was rushed to the hospital but he had recovered consciousness at the time of admission When seen by us he was still a little weak. He stated that he had been unconscious about fifteen minutes and the attack was preceded by a feeling as if his head were bulging He had vomited during the unconsciousness. The blood pressure was 140 mm systolic and 85 mm diastolic.

Electrocardiogram was normal except for slight left axis deviation He was given a trial of digitalis but it did not seem necessary to continue this When he was last seen February 25 1932 he was in good condition The blood pressure was 160 mm systolic and 90 mm diastolic

Case III.—The third case was a woman of sixty years first seen by us August 26 1930 In April 1930 she had had an attack of oppression in the midchest on exertion and after dinner about this time she had had severe substernal pain radiating toward the left arm lasting for an hour Her father had one brother who died suddenly

Physical examination showed her to be somewhat overweight. Her face was rather flushed There was slight arcus senilis and the retinal vessels were small The apex impulse of the heart was in the fifth space, 10 cm to the left of the midsternal line and 1½ cm beyond the midclavicular line. The sounds were of good quality There was a slight apical systolic murmur The rhythm was regular at a rate of 120 and the blood pressure was 190 mm systolic and 110 mm diastolic.

Electrocardiogram showed sino-auricular tachycardia with inversion of the T wave in lead III She improved with rest and theominal and was seen at intervals until November 6 1931 At that time she complained of some lower substernal distress waking her in the morning and interfering with walking The pain rarely radiated to the left arm and shoulder blades A cousin had died of angina pectoris shortly before this visit.

Examination showed no change in the heart The blood pressure was 190 mm systolic and 110 mm diastolic. Electrocardiogram showed normal rhythm rate 90 slight slurring of the Q R S complexes and slight left axis deviation She complained of slight substernal oppression during the examination Although she had carried nitroglycerin tablets for some time she had never tried them and it was suggested then that she discover its effect on the pain She put 1/200 grain under her tongue and was observed for about five minutes. During this time she had no uncomfortable sensation and the pain apparently disappeared She walked to the waiting room where she was to wait for her automobile and about ten minutes after the tablet was taken she tottered back to the examining room where she fainted broke out into a cold sweat and the heart became slow although not markedly so.

The blood pressure dropped to 110 mm systolic and 80 mm diastolic With the use of aromatic spirits of ammonia she recovered in about twenty minutes although she continued to feel quite weak. The blood pressure rose in this time to 135 mm systolic and 90 mm diastolic She was admitted to the hospital for the night and discharged the next morning feeling well The blood pressure was 150 mm systolic and 90 mm diastolic It is interesting that on December 17, 1931, when she was reexamined the systolic blood pressure was still 25 mm lower than it was before the fainting attack When she was last seen April 4, 1932, she was feeling quite well and the blood pressure was only 150 mm systolic and 90 mm diastolic The heart was slow and regular with good sounds

CONCLUSIONS

The profound effect from nitroglycerin such as was seen in these 3 cases would certainly be of potential if not actual danger to many patients Sudden change in the systemic blood pressure of patients with hypertension or arteriosclerosis puts a severe strain upon the arterial system especially in the brain and heart, and the marked drop in pressure in cases of beginning or impending coronary occlusion probably favors thrombosis in the artery On the other hand, we have observed 900 cases of angina pectoris in private practice, most of whom have been given prescriptions for nitroglycerin In only these 3 cases, one of whom did not have angina, have we, ourselves, experienced any harmful result from the use of therapeutic doses

However, it is an easy routine procedure in the office to try out the effect of nitrites upon patients for whom they are advised and we believe that nitroglycerin should be given sublingually in doses of 1/400 to 1/200 grain to such patients under observation to avoid serious collapse from its use in situations where such an effect might be dangerous

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CLINIC OF DR CONRAD WESSELHOEFT

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MUMPS MENINGO-ENCEPHALITIS

So much is being said about the diagnosis of preparalytic poliomyelitis that it is well to present a case of mumps meningo-encephalitis

This boy[1] of eight came down with a mild attack of mumps nine days ago The parotid swelling subsided, and all went well until the sixth day of convalescence when with no history of injury he became feverish complained of headache and vomited in the afternoon and again during the night. The family physician noticed an increasing rigidity of the neck and spine, and for this reason the patient was hurried to this hospital

On admission three days ago the child was very drowsy with occasional short periods of restlessness. There was no difficulty in swallowing and he took liquids well The eyes were closed or half closed when drowsy and staring when restless. The pupils were equal and reacted to light There was no evidence of any paralysis of the eye muscles and no nystagmus. No swelling of the parotid sublingual or submaxillary glands could be detected The openings of Stenson s and Wharton s ducts were not remarkable. The face was flushed Temperature, 104 6 F pulse 132 respiration 34 There was a well marked rigidity of the neck and spine When one attempted to raise the head with the child lying on the back, the entire body was lifted and this was accompanied by pain In the sitting position it was impossible for the child to put his head between his knees or touch his chin to his knees The spine was stiff without opisthotonus and the entire back was tender No tremors were seen. There was a slight Brudzinski and a moderate bilateral Kernig The knee jerks were diminished and equal ankle clonus and Babinski absent as well as the Gordon and Oppenheim. The abdominal and cremasteric reflexes were present the testicles being normal A very pronounced *tache cérébrale* was present. The ears were entirely negative. There was no nasal discharge, and the throat showed only a slight injection of the fauces. A few very small glands could be felt in the neck. Nothing abnormal could be elicited in the heart and lungs and the abdomen was negative on palpation In short here was a well-developed well nourished boy obviously acutely sick, one week after the onset of mumps with no other symptoms than those attributable to an acute meningo-encephalitis.

[1] Hospital No 23 707 demonstrated in the graduate course in pediatrics Harvard Medical School, 1932

A white count showed 9000 leukocytes, with 25 per cent polymorphonuclears and 75 per cent lymphocytes Lumbar puncture showed a slightly hazy fluid of the "ground glass" variety under a normal pressure of 6 mm Hg Twenty cc of spinal fluid were drained off and immediately examined The cell count was 1420, "mostly lymphocytes" Sugar and globulin were both present A culture of the spinal fluid is reported as showing "no growth" The urine is negative

To complete the record one must mention that he had pneumonia at the age of one, and that he has had measles, chickenpox, and whooping cough

Today you see this cheerful boy with no complaints The temperature, pulse, and respiration are normal There is no rigidity of the neck, and he can, as you can see, sit up in bed and put his head between his knees What his spinal fluid would show now if we made another lumbar puncture would be of purely academic interest, but from the work of others we learn that the cell count drops to 50 or below within ten days [1] There is no suggestion of any paralysis

In view of the occurrence of these meningeal symptoms during convalescence from mumps, and in view of the symptoms, the laboratory findings, and the prompt recovery, we may now conclude that this has been one of those rare cerebral complications of mumps, a true meningo-encephalitis

You will note that in recording the history and physical findings I have followed the chronological order of the clinical notes We knew the child was convalescing from mumps, consequently, it was necessary to keep in mind the features of mumps which might have some possible bearing on the situation, and at the same time to keep before us those other diseases which could, of course, appear on the sixth day of mumps I would remind you that a lobar pneumonia can be overlooked on account of the predominance of meningeal symptoms not at all unlike those presented in this case Hence the importance of the negative chest findings The remote possibilities are quickly covered in the course of any such flexible order of examination, and how much easier all this is in the hospital than in the home! The white count was being done during the physical examina-

[1] Weissenbach, R J , Basch, G , and Basch, M La méningo-encéphalite ourlienne primitive Signification des alternations du liquide céphalo-rachidien dans l'infection ourlienne Paris Méd , July 27, 1930, 1, 533

tion, and the cell count of the spinal fluid was reported only a few minutes after the lumbar puncture I should like to emphasize the fact that the facilities of a hospital permit the assembling of essential data for diagnosis much more rapidly than at the home Furthermore, if specific treatment is shown to be indicated, this is at hand You must bear in mind that while today we have the advantage of all these accumulated facts before us, the family physician and the parents were anxiously awaiting our verdict day before yesterday, when this boy was admitted

In this instance the family physician, Dr A B Toppan was unusually keen in his appreciation of the symptoms of preparalytic poliomyelitis, because he had lived through an epidemic of poliomyelitis the previous year in Watertown where this child came from Furthermore, this physician was aware of the term "mumps meningitis" Consequently, the case was referred to the hospital within twenty four hours of the onset of the meningeal symptoms as a possible preparalytic poliomyelitis, with a question as to mumps with meningeal involvement On arrival at the hospital the patient presented the classical symptoms of preparalytic poliomyelitis Against this diagnosis was the circumstantial evidence that the child was recovering from mumps, and further, that this is the middle of winter The former far outweighs the latter, because acute poliomyelitis can occur in winter The temperature was unusually high for poliomyelitis Other complications of mumps are capable of giving fever and vomiting, such as orchitis in an undescended testicle, or pancreatitis, but both of these are attended by acute abdominal pain Acute nephritis with uremic symptoms can occur in the course of mumps [1] [2] There was no evidence of further involvement of the salivary glands This is mentioned because Comby[3] records successive involvement of one salivary gland after another with four days intervening

[1] Schottmüller H Parotitis Epidemica Nothnagel s Specielle Pathologie und Therapie, Vienna 1904 3 2 61
[2] Rubrah J Abt s Pediatrics, 1925 vol 6 286
[3] Comby J Les Oreillons Paris, 1893 67

Anyhow, we should not expect this recrudescence in these glands a week after the initial parotitis

In this case, however, the whole picture was one of meningeal irritation With this point established early in the examination a lumbar puncture was in order I am particularly opposed to doing a lumbar puncture unless obvious symptoms of meningeal irritation are present Here the classical symptoms of rigidity of the neck and spine warranted the puncture for diagnostic purposes Rigidity of the neck and spine, however, are not always present in these cases Other symptoms (such as convulsions, tremors, and even delirium) may indicate a lumbar puncture The fluid findings were those of acute poliomyelitis, and also those of mumps meningo-encephalitis In the early stages of tuberculous meningitis the fluid is clear and with a comparatively low cell count—rarely over 100, the lymphocytes predominating Tubercle bacilli may be found in the fibrin film In early lethargic encephalitis the cell count is also relatively low, but in other respects does not differ from "mumps meningitis" Syphilitic meningitis and meningitis from lead poisoning need only be mentioned here as having similar cell counts The cell count in the case presented this morning is unusually high for mumps meningo-encephalitis In fact, it is higher than any I have found mentioned in the literature Counts of 900[1] and 1000[2] have been recorded In some cases the cell count is below 100, but it is more apt to be from 200 to 500 [3]

Globulin is usually present and sugar almost invariably Consequently, the spinal fluid findings in mumps meningo-encephalitis are the same as in poliomyelitis, both being caused by filterable viruses In the other conditions mentioned above, the spinal fluid is of little diagnostic value when the count is low, except for the finding of tubercle bacilli, a positive Wassermann, and a positive lead test In cerebrospinal meningitis and

[1] Casparis, H R Cerebral Complications of Mumps, Amer Jour Dis of Child, 1919, 19, 190

[2] Weissenbach, R J, Basch, G, and Basch, M Le *méningite* et la meningo encéphalite ourliennes primitives Anal de Méd, 1930, 27, 1, 27

[3] Haden, R L Cerebral Complications of Mumps with Report of Nine Cases, Arch Int Med, 1919, 23, 739

in other pyogenic infections of the meninges, the spinal fluid presents such different pictures that we need not go into their differentiation

The blood count in this case was of help from a negative standpoint There was a moderate leukocytosis with a relative lymphocytosis This is what we might expect to find in mumps, with or without meningo-encephalitis, and in poliomyelitis In both latter conditions the blood findings are very variable A leukocytosis as high as 19,000 was reported by Haden,[1] and in a fatal case of this same author's the count was 12,000 with 86 per cent neutrophils

The last previous case of mumps meningitis on this service was on June 5, 1929

This case was a boy[2] of four with subsiding bilateral parotitis.[3] He had had one convulsion at home, and on admission showed convulsive twitchings of both arms and both legs, and spastic extension of the fingers. There was rigidity of the neck and spine a marked *tache cérébrale* and profuse perspiration He was extremely restless, thrashing about in his crib He had been given 15 grains of bromides at home without any appreciable quieting effect. Restlessness continued in spite of ½ grain of phenobarbital and 1/24 of morphine. At the lumbar puncture on admission the spinal fluid was clear and spurted out in a stream The cell count was 570 lymphocytes 63 per cent and neutrophils 27 per cent At the second lumbar puncture on the second day the flow of fluid was not increased cell count 426 lymphocytes predominant. He became quiet soon after the second lumbar drainage and on the third day the temperature had dropped from 102 to 99 F and thereafter he was bright and quite normal in every way

In the diagnosis of mumps meningo-encephalitis there are two factors of great importance One of these is what I have called circumstantial evidence, namely, the existence of mumps But the fact that the patient does not have any parotid involvement or is not recovering from the same does not preclude the existence of this disease, because there are no less than 21 cases on record[4 5 6] in which the meningeal symptoms pre-

[1] Haden R. L. Loc. cit.
[2] Hospital No 20 602
[3] Day of disease unknown
[4] Casparis 1919
[5] Walker F D Case of Mumps with Cerebral Complications U S Naval Med Bull., 1925 23 42
[6] Weissenbach et al Anal de Méd 1930 26

ceded those of the salivary glands in the same way as an orchitis may be the primary manifestation Of course, these instances are very rare, but they emphasize the importance of ascertaining the existence of even a possible exposure to mumps Indeed, cerebral complications of mumps are in themselves rare

As a matter of fact the incidence of this condition is difficult to ascertain from the literature Dopter[1] found evidence of meningeal involvement in 9 8 per cent of 1705 cases of mumps under his care, while Roux[2] is reported as having found a similar evidence in only 1 per cent In the United States Haden found 9 cases among 475 at Camp Lee, while Radin[3] mentions "convulsions" in 1 case but no other definite signs of central nervous system involvement in recording the complications of 5756 cases at Camp Wheeler At this hospital we have had only these 2 cases among 824 of mumps

The second factor in the diagnosis is one which develops rapidly in the course of the case, namely, the prompt and rather sudden recovery This statement needs qualification, because cases of slow recovery are on record, and there are also cases which do not recover, fortunately, these are very few In preparalytic poliomyelitis the recovery is apt to be slower, particularly as regards the rigidity of the neck and spine In mild cases of poliomyelitis this rigidity may disappear quickly, but when it is so marked as in this case of mumps we have had before us, we should expect to find rigidity persisting longer, and also a more gradual subsidence of fever

The similarity of the symptoms and laboratory findings in mumps meningo-encephalitis and preparalytic poliomyelitis is so obvious that they need not be recounted in detail Furthermore, it is of interest to note that in the former we may have a so-called "dromedary" type, as in the latter, that is, the meningeal symptoms may subside and flare up again in three or

[1] Dopter, C La méningite ourlienne, Paris Med , 1910, 1, 35

[2] Synge, V M Mumps Meningitis, Irish J M Sci , July, 1930, 290

[3] Radin, M J Epidemic of Mumps at Camp Wheeler, Arch Int Med , September, 1918, 22, 354

five days [1] In mumps this is apparently not so serious an omen as in poliomyelitis, because in the former the relapse is milder than the original In our 1929 case the convulsions and spasticity of the fingers do not suggest poliomyelitis, but these conditions may occur in this disease, and when they do recovery is not likely to be rapid as it was in our case

Although I have stressed this factor of sudden recovery we must bear in mind that serious consequences of mumps encephalomeningitis may result Thus we may have paralysis of cranial or spinal nerves Strabismus and pupillary changes have been reported, as well as temporary paralysis of the face and of the extremities, sometimes in the form of hemiplegia Dopter[2] has emphasized the benign and often transitory character of the effects on both the cranial and spinal nerves which result from "penetration of the serofibrinous exudate into the nerve trunks at their origins" The two notable exceptions to this are when the optic and auditory nerves are attacked, where atrophy is apt to follow with its disastrous consequences Aphasia and protracted disturbance of the emotional tone have been reported as following these cerebral complications Palatal paralysis, however, is not mentioned The rarity of localized complications of the nervous system may be gathered from the statement of Massary[3] to the effect that none were observed in a series of 1835 cases of mumps

In those cases which are fatal, death comes on as it does in encephalitis Nowhere have I found anything to suggest respiratory paralysis, either of the bulbar or spinal type, such as we see in poliomyelitis Autopsy findings show a serous meningo encephalitis [4] In four autopsies by Gordon[5] meningeal con

[1] Dumitrescu T Jonnesco C and Chiser S Parotidite épidemique avec méningite et orchite concomittantes Bull et Mém Soc. Méd d Hôp de Paris, 1923 48 481 Weissenbach et al. Annal de Méd 1930 10

[2] Dopter 1910 38

[3] Massary M E. de (Discussion) Bull et Mém Soc. Méd d Hôp de Paris, 1929 53 817

[4] Larkin W F Mumps Meningitis Report of Two Cases with Autopsy Findings Military Surg 1919 64 92

[5] Gordon M H On a Fatal Illness in Children Associated with Acute Interstitial Parotitis Lancet London 1913 2 275

gestion was constant, the spinal fluid was clear, and contained an excess of lymphocytes In two of these there was flattening of the convolutions Careful search in all 4 cases failed to reveal, either in the cord or in the cortex, the infiltrative lesions so characteristic of poliomyelitis In 2 cases the lymphoid tissue in the small intestine was more prominent than usual In 1 case this was particularly marked in Peyer's patches, and in another in the solitary follicles The lymphatic glands of the neck and mesentery were swollen This involvement of the lymphatics is similar to the findings in poliomyelitis

Thus, throughout this discussion we find a similarity between poliomyelitis and mumps meningo-encephalitis Such differences as exist depend on the fact that in poliomyelitis the pathologic picture is one of meningo-encephalo-poliomyelitis, whereas in mumps it is a meningo-encephalitis In the preparalytic stage of the former the clinical similarity of the two conditions is pronounced

The treatment should be directed against the mechanical dangers of intracranial pressure Spinal drainage is the most logical step in the way of affording relief Whether it needs to be "forced," as practiced by Retan[1] in other infections of the central nervous system, must depend on the severity of symptoms met with The failure to utilize spinal drainage at all, or insufficiently, in the fatal cases recorded is worthy of note

The use of convalescent mumps serum should be considered, and in view of the wide prevalence of acquired immunity to mumps, a normal adult serum, or any convalescent adult serum, might be useful On the other hand, the prognosis in these cases is so good that it seems advisable to depend on spinal drainage, since an abrupt recovery is to be expected on the third day

[1] Retan, G M Forced Spinal Drainage in Its Relation to Infections of the Central Nervous System, Jour Amer Med Assoc , September 3, 1932, 99, 10, 826

CLINIC OF DR HARRY BLOTNER

PETER BENT BRIGHAM HOSPITAL

THE TREATMENT OF DIABETES

IN this clinic, today, I shall present 2 patients in order to illustrate certain phases of the modern treatment of diabetes I wish to discuss, particularly, methods of treatment that can be utilized in the management of cases which do not require hospital care

CASE I.—The first patient Mrs D C. is an American housewife fifty four years old She was admitted to the Out Door Department of the Peter Bent Brigham Hospital on September 28 1931 just about a year ago. Her family history is important possibly in that two sisters and a grandmother died of tuberculosis. She has been married for thirty-one years and has 4 children living and well In 1907 she had typhoid fever but otherwise has had no serious illness. She went through the menopause ten years ago uneventfully

Nine years ago she weighed 145 pounds and felt perfectly well Then for no apparent reason she became excessively thirsty began to pass a large quantity of urine and soon noticed pruritus vulvae Because of the persistence of these symptoms she visited a doctor two years later and he discovered that she had diabetes. He advised her to eat a very restricted diet She dieted carefully for several years being sugar free most of the time. However the diet was so strict that she lost weight little by little and became so weak and discouraged that finally she decided to give up all dieting The result was that she became weaker than ever and had a return of all her previous symptoms. It was on this account that she came to the hospital

She then weighed only 99 pounds (45 Kg) making her more than 50 pounds underweight for her age and height The general physical examination was not remarkable except for moderate tortuosity of the retinal arteries and a few old hemorrhagic areas in both fundi. There was but little evidence of peripheral vascular disease and the blood pressure was 144/100 *x* Ray films of the chest showed no signs of pulmonary tuberculosis—an important diabetic complication to exclude in a patient with her family history The urine contained a large amount of sugar

Here was an emaciated and feeble diabetic patient who needed, obviously, food by which to regain strength and weight For this reason, the immediate use of insulin was indicated, for ordinarily the most common factors for prescribing insulin treatment to diabetics are malnutrition, weakness, infection, acidosis, or the persistence of sugar in the urine after the patient has attempted to eat an adequate diet without the help of the drug

On the day of her first appearance in our Diabetic Clinic, therefore, she was taught how to test for and to keep a record of the urinary sugar, how to take insulin and how to estimate a diet This sounds like a complicated program, but in reality is a comparatively simple one, and feasible to complete without hospitalization

She was taught to test for sugar in the urine according to specific directions and these directions she was made to learn by heart Put a teaspoonful of Benedict's solution in a test tube and add to that 8 drops of urine Then place the tube in a small pan or tin cup containing boiling water for five minutes If the urine is sugar free, the solution will remain clear blue If sugar is present, the color will vary from an opaque green to an orange red depending on the concentration of sugar in it That the test may be of some quantitative value is shown by the fact that when it is performed according to the method described, a "green test" means a concentration of less than 1 per cent sugar, a "yellow test" represents a concentration of 1 to 2 per cent sugar and a "red test" indicates a concentration of over 3 per cent sugar in the specimen of urine examined

She likewise was taught to inject herself with insulin, also, according to the following specific instructions First wash your hands with soap and water The cylinder and plunger of the glass syringe and a wired hypodermic needle are now placed in a pan of cold water This is brought to a boil, and the syringe and needle are boiled for five minutes Pour the water off and allow the syringe to cool Place the needle on the syringe and remove the wire, being careful not to touch the end of the needle with your fingers Wipe the rubber cap of the insulin bottle with alcohol Withdraw the plunger from the barrel of

the syringe so that the syringe contains a little air Pierce the rubber stopper of the insulin bottle with the needle Force the air in the syringe into the bottle to avoid a vacuum Invert the bottle and withdraw the desired amount of insulin Decide where to make the injection on the thigh and clean the region with alcohol Grasp the skin firmly between your thumb and index finger, insert the needle through the skin and make the injection Withdraw the needle and syringe and again cleanse the area with alcohol After the injection is made, rinse the

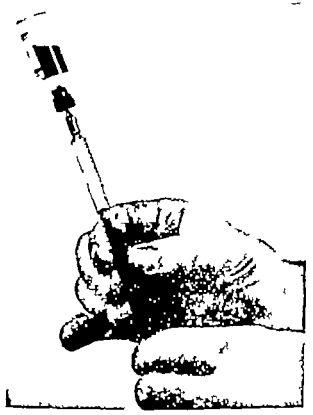

Fig 168 —A patient measuring insulin

needle and syringe with water and dry them, reinserting the fine wire into the needle

Insulin is measured by units It is made up in four concentrations so that each cubic centimeter contains either 10, 20, 40 or 80 units They are called U-10, 20, 40, and 80 insulin respectively To measure 10 units of insulin, one can take 1 cc of U 10 insulin or ½ cc. of U 20 insulin and so on For ordinary use, U 20 insulin is most convenient

Finally she was given a written diet telling her what to eat

for breakfast, dinner, and supper, and a list of 3 and 6 per cent vegetables, 10 per cent fruits, and of various foods with their values so that she could have a reasonably wide range from which to select Nowadays, as you know, the diabetic diet is much more liberal than it was and contains green vegetables, fruits, eggs, bacon, meat or fish, butter, milk, cream, cheese,

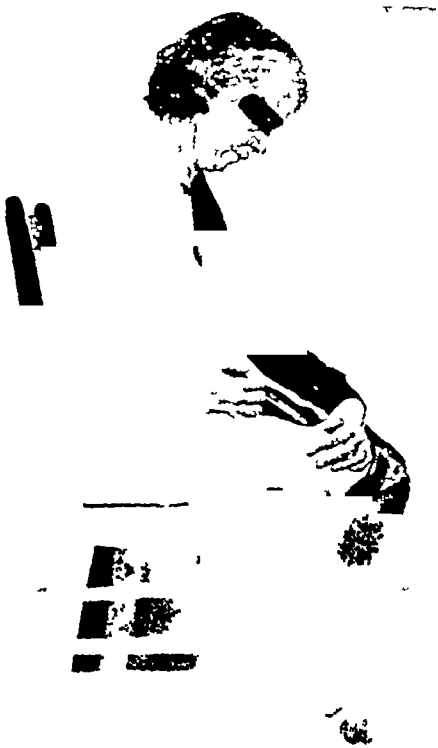

Fig 169 —A patient injecting herself with insulin

olive oil, cereals, and Uneeda biscuits Occasionally bread and potatoes and even sugar are added Table 1 gives the carbohydrate, protein, and fat content of the common diabetic foods

It seemed desirable for the patient to eat at the outset approximately 2100 calories a day, containing around 120 Gm of carbohydrate, 70 Gm of protein, and 150 Gm of fat Why was this diet prescribed? This particular patient was so thin

TABLE 1

THE CARBOHYDRATE PROTEIN AND FAT CONTENT OF COMMON DIABETIC FOODS[1]

Foods.	Amount.		Food value in Gm			
	Household measures.	Weight in Gm.	Carbohydrate	Protein	Fat.	Calories.
Vegetables, 3 per cent	1 sauce dish	150	5	3	0	32
Vegetables, 6 per cent	1 sauce dish	150	10	3	0	52
Fruit, 10 per cent	1 orange or ½ grapefruit	100	10	0	0	40
Cooked cereal	½ cup	120	24	4	0	112
Dry cereal	1 cup	20	15	1	0	64
Shredded wheat	1 biscuit	30	23	3	0	104
Uneeda biscuits	2 crackers	12	10	1	1	53
Bread	1 slice	30	18	3	0	84
Potato	1 medium	120	24	4	0	112
Milk	1 glass	200	10	7	8	140
Cream, 40 per cent	⅛ cup	120	4	4	48	464
Cream, 20 per cent	⅔ cup	120	4	4	24	248
Butter	1 teaspoonful	5	0	0	4	36
Oil (except mineral oil)	1 tablespoonful	15	0	0	15	135
Cheese (American)	1 inch cube	30	0	8	11	131
Bacon (crisp)	4 lean strips	30	0	5	15	155
Meat fish or chicken	1 medium serving	90	0	21	9	165
Egg	1	45	0	6	6	78

[1] 1 Gm. protein = 4 calories. 1 Gm. carbohydrate = 4 calories. 1 Gm. of fat = 9 calories.

that she needed calories with which quickly to gain weight and strength For her age and height she should weigh, theoretically, about 150 pounds (70 Kg) A ration of 30 calories per Kg of normal weight would give her a very high calory diet at her present level of weight, but because of emaciation and weakness, it seemed advisable to encourage her to eat an unusually liberal diet Accordingly a diet containing 30 calories per Kg of normal weight was chosen Her normal weight being 70 Kg, she was prescribed 70 × 30 = 2100 calories per day This was arranged to contain definite amounts of carbohydrate, fat, and protein The carbohydrate fraction in the diet was limited to 120 Gm —a reasonable quantity, allowing her each day plenty of fruit and green vegetables, a certain amount of cereal, bread, and milk, but excluding sugar or too much concentrated starch-containing foods The régime of 70 Gm. of protein, too, was an arbitrary one, high enough to allow reasonable helpings of egg and meat each day, but on the other hand not in sufficient quantity to be at all harmful The amount of fat to be used was determined by arithmetic 120 Gm

of carbohydrate produced 120 × 4 = 480 calories, and the 70 Gm of protein 70 × 4 = 280 calories, a total of 760 of the 2100 calories This leaves 2100 − 760 = 1340 calories to be furnished by fat Since 1 Gm of fat yields 9 calories, it required 1340 divided by 9 = 150 Gm of fat to complete the diet Various authorities nowadays would consider such an amount of fat too large It is my belief, however, that there is as yet no proof that such an amount of fat is harmful

The next step was to fill the prescribed diet in a manner that she could understand easily This was done by writing on a piece of paper an approximate list of daily amounts of food to be eaten with their carbohydrate, protein, and fat contents These values were calculated from the preceding table

TABLE 2

A Preliminary List of Foods for the Day

Foods	Household measures	Weight in Gm	Carbohydrate.	Protein	Fat
Vegetables 3 per cent	4 saucers	600	18	10	0
Cooked cereal	½ cup	120	24	4	0
Cream 40 per cent	½ cup	120	4	4	48
Eggs	2	90	0	12	12
Butter	3 tablespoonfuls and 1 teaspoonful	50	0	0	42
Milk	½ cup	120	6	4	4
Meat	1 moderate serving	120	0	28	12
Oranges	3	300	30	0	0
Bread	2 slices	60	36	6	0
Mayonnaise	2 tablespoonfuls	30	0	0	30
		Total	118	68	148

If, after making up such a list, the carbohydrate, protein or fat totals more or less than the prescribed amount, varying quantities of food are either subtracted or added to fill the dietary prescription more accurately

This allowance of food was apportioned into three meals so that each contained one third of the total amount of carbohydrate The portions of the protein and fat were divided more roughly to suit the various meals Table 3 is the diet list after it had been revised, and is the one first given her to follow

As you can see, this diet is palatable enough to be followed for a long period of time without impatience It is of only

TABLE 3

THE PATIENT'S DIET

Breakfast	*Amount*
Orange or grapefruit	1 ½
Cooked cereal or cornflakes	½ cup 1 cup
Egg	1
Butter	1 tablespoonful
Milk	½ cup
Dinner	
Lean meat or fish or chicken	1 serving (4 oz.)
3 per cent vegetables or 6 per cent vegetables	2 saucers 1 saucer
Bread	1 slice
Butter	1 tablespoonful
Mayonnaise	1 tablespoonful
Orange	1
Supper	
Egg	1
3 per cent vegetables or 6 per cent vegetables	2 saucers 1 saucer
Bread	1 slice
Butter	4 teaspoonfuls
Mayonnaise	1 tablespoonful
Orange	1
Heavy cream (40 per cent) for the day	½ cup
Clear soup tea or coffee without sugar or additional cream as desired	

approximate accuracy, but gone, thank goodness, are the days of elaborate food scales, weighing, and turmoil for the patient with diabetes. Simplicity in treatment is the goal, so that any diabetic patient can now eat just about as does the rest of the world, perhaps with more discretion and judgment, but without being "different" and isolated.

Imagine, now, the patient ready to start on her travels. She has learned how to test for sugar in the urine; she has been supplied with a bottle of Benedict's solution, a test tube, and a medicine dropper and has demonstrated to our satisfaction that she knows how to use this equipment. She has a diet list telling

her what to eat for breakfast, dinner, and supper We know about how many grams of carbohydrate, protein, and fat it contains, and how many calories She only understands that she *must stick to it* until ordered otherwise, and has promised to do so She has an insulin syringe, a few needles, and a few bottles of U-20 insulin She has gone through the motion of measuring insulin (from an old insulin bottle filled with water) so that she can measure any number of units that she is asked to She has injected a measured dose (into a pincushion) so that she knows what it feels like to manipulate the syringe She has been warned about insulin reactions and what to do about them should she have any Just before she goes home, we give her an injection of 10 units and instruct her to take 10 units three times a day, about half an hour before each meal This dose is to be diminished a unit or two per dose if reactions occur, but is not to be increased She is to test her urine once a day and return to us in five days with a record of what has happened

TABLE IV

THE REPORT OF URINE TESTS FOR SUGAR AS GIVEN BY A PATIENT ON INSULIN THERAPY

Date	Result of Benedict's test
September 29, 1931	Red
September 30, 1931	Yellow
October 1, 1931	Blue
October 2, 1931	Yellow
October 3, 1931	Green
October 4, 1931	Blue
October 5, 1931	Blue
October 6, 1931	Blue
October 7, 1931	Green
October 8, 1931	Blue

You can see how relatively simple it is for a patient to learn to take the insulin treatment Hospitalization and elaborate laboratory equipment are usually unnecessary All that is needed is a little cooperation and common sense

This patient has returned to the clinic from time to time during the past year and the following is a summary of her record

TABLE 5

A DIABETIC TREATED WITH INSULIN FOR TWELVE MONTHS

Date	Urinary sugar	Units of insulin.	Weight in pounds	Diet
Sept. 29 1931	++++	10-10-10	99	C 120 P 70 F 150
Oct 8	0	10-10-10	103	
Oct 29	0	10-10-10	108	C 160 P 70 F 150
Nov 19	S P T	10-10-10	111	
Dec. 15	0	10-10-10	114	
Jan 14 1932	++	10-10-10	118	
Feb 26	0	10- 0-10	120	
April 6	0	10- 0-10	123	C 180 P 70 F 150
June 24	0	10- 0- 5	126	
Sept. 20	0	10- 0- 5	126	

She has gained 27 pounds in weight and feels very much stronger than she did The amount of insulin which she requires has been reduced and her diet has been increased She has rarely shown a trace of sugar in the urine

Case II.—The second case, Mrs G T is a Jewish housewife, forty five years old She entered the Out Door Department of the Peter Bent Brigham Hospital on March 18 1925 nearly seven and one-half years ago Her family history is unimportant. She has been married for twenty years, and her husband and 2 children are living and well In the past she has always been unusually well

Ten years ago she weighed 160 pounds but shortly before entry there had been a loss of 15 pounds.

A short time before coming to us she went to a dentist who told her that he suspected there was something wrong with her urine because her gums were swollen Soon she became weak and very thirsty and began to drink lots of water On this account she came to our clinic.

She weighed 146 pounds (66 4 kg) making her 16 pounds overweight for her age and height The general physical examination was not remarkable except for a pendulous abdomen and a liver edge which was palpable 1 cm below the costal margin The blood pressure was 155/80 The urine contained a large amount of sugar

In contrast to the first patient, here was an obese diabetic patient who needed to lose, rather than to gain weight, and who needed a restricted diet instead of a liberal diet with insulin Consequently, she was ordered to take a low calory diet which contained about 60 Gm of carbohydrate, 60 Gm of protein,

and 100 Gm of fat, making a total of 1380 calories, that is, 20 calories per Kg of her body weight The diet was constructed as in the first case Here is the list of food given her to eat

TABLE 6

THE SECOND PATIENT'S DIET

Breakfast	*Amount*
Orange	½
cooked cereal or	¼ cup
Cornflakes	½ cup
Egg	1
Bacon	4 strips
Dinner	
Lean meat, fish or chicken	1 serving (4 oz)
3 per cent vegetables or	2 saucers
6 per cent vegetables	1 saucer
Butter	1 teaspoonful
Orange	1
Supper	
Egg	1
3 per cent vegetables or	2 saucers
6 per cent vegetables	1 saucer
Butter	2 teaspoonfuls
Orange	1
Heavy cream (40 per cent) for the day	⅓ cup

This patient was taught how to make bran cakes These cakes are of help to patients eating low calory diets but are rarely necessary after the carbohydrate reaches more than 100 Gm per day

This diet differed chiefly from the first patient's in that it contained no bread or milk and the fat content was 50 Gm less However, the diet still contained a reasonable allowance of fruit, vegetables, cereal, eggs, meat, and fat each day Had the patient not felt satisfied with this diet, or had she shown sugar constantly, insulin would have been prescribed, with a diet more liberal in carbohydrate but containing no more calories

The patient was taught how to test her urine and was asked

to return to the clinic in two weeks' time bringing a record of her urine tests Here is her report

TABLE 7

THE RECORD OF URINE TESTS FOR SUGAR AS REPORTED BY THE SECOND PATIENT ON A DIET OF C 60 P 60 F 100

Date.	Result of Benedict's test
March 19 1925	Red
March 20 1925	Yellow
March 21 1925	Yellowish green
March 22 1925	Green
March 23 1925	Yellow
March 24 1925	Green
March 25 1925	Blue
March 26 1925	Blue
March 27 1925	Yellow
March 28 1925	Blue
March 29 1925	Green
March 30 1925	Green
March 31 1925	Blue
April 1 1925	Blue
April 2 1925	Blue

She has been under observation for over seven years and has progressed satisfactorily as far as the diabetes is concerned We have been able to reduce her weight slowly, making her lose 20 pounds, and after some time to increase her diet little by little She has shown sugar only when she has overeaten and on such occasions has been able to become sugar free very easily by a little self discipline. Table 8 is a summary of this patient's record

Students and doctors occasionally ask how often the blood sugar concentration should be determined in the treatment of diabetics, believing that it is necessary to make this test frequently in order to give their patients the best advice Routine blood determinations are not necessary Here are 2 patients who illustrate how rarely the blood sugar level needs to be determined. In the first case only one blood sugar test was made in one year of treatment and in the second case only two blood sugar determinations were made in seven and one-half years of treatment, both cases progressing in a perfectly satis-

TABLE 8

THE PROGRESS OF THE SECOND PATIENT ON A DIET DURING SEVEN YEARS OF PERIODIC OBSERVATION

Date	Urinary sugar	Weight in pounds	Diet	Remarks
March 18 1925	++++	146	C 60, P 60, F 100	
April 2	0	145		
May 27, "	0	142½	C 80, P 70, F 100	Feels better
Sept 30	0	143	C 95, P 75, F 100	
Dec 16 "	+	142		
Feb 3, 1926	0	144		
April 7 "	++	148	C 80, P 70, F 100	Patient has been overeating Feels well
April 28	0	146		Feels well
July 14, "	0	140	C 90, P 70, F 100	Feels well
Nov 3	+	141		
Jan 19 1927	+++	142		Overeating
March 30 "	0	139½		Feels well
May 25 "	0	137½		Rarely shows sugar at home.
Sept 4 "	0	136		Feels well
March 28 1928	0	138	C 100, P 70, F 100	Sugar free at home right along
Jan 23, 1929	0	137		Rarely shows sugar
Oct 30 "	+	134		
Dec 11 "	0	131	C 120 P 70 F 100	Feels somewhat weak
Feb 19 1930	0			
Aug 13, "	0	128	C 140, P 70 F 100	Has no complaints
Nov 12, "	+	128		
Dec. 17, "	0	128		Feels well.
April 8 1931	0	127		No complaints
Sept 30 "	0	126½		Had tooth extracted
Oct 6 "	+++	127		
Jan 18 1932	+	128		Feels well
March 2, "	0	128		
May 4, "	0	127		

factory fashion These tests were made because of academic interest rather than necessity This is important to emphasize Doctors who do not have access to laboratories with elaborate equipment can treat most cases of diabetes satisfactorily with nothing more than a knowledge of how to use properly a diet list, insulin and Benedict's solution

To summarize, in this clinic I have presented 2 patients with diabetes, one having been treated with insulin and the other without insulin Both have been treated as out-patients and neither has lost any time because of the treatment These cases illustrate what satisfactory results usually are obtained in the management of diabetes

Diabetic therapy now can be made very simple, hospitalization of all patients with this disease is by no means essential, and elaborate laboratory equipment is usually unnecessary for good results provided that the patients are cooperative and how reasonable intelligence in carrying out their instructions

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PERIPHERAL COMPLICATIONS OF ULCERATIVE COLITIS

AT a time when a more general recognition is developing of the frequent occurrence of so-called "deficiency symptoms it is important to visualize a little more clearly the mechanism that underlies their production It is obvious that symptoms due to a lack of important food substances must arise either because of an insufficient intake of such substances, an improper absorption from the alimentary tract of these substances, or a too rapid elimination The rôle of a specific vitamin lack in such diseases as scurvy, rickets, and xerophthalmia and probably in beriberi and pellagra is well established Pernicious anemia, with its insufficient gastric secretion, and consequent lack of proper hematopoiesis, is becoming more completely visualized, although the mechanism of subacute combined cord degeneration is still but imperfectly understood Sprue in a similar fashion has been shown to be due in large part at least to a disturbance similar to that existent in pernicious anemia and responds more or less satisfactorily to similar therapy Hypochromic anemia, not due to hemorrhage, and nutritional edema are known to be associated with a lack of iron and protein respectively

There are many diseases, however, in which the deficiency symptoms occur inconstantly and are not of necessity a characteristic of the underlying condition Under these circumstances the symptoms are in a sense a complication, and as such are frequently overlooked or recognized at altogether too late a period This is particularly true in conditions that may eventually require surgery Prompt recognition of the potential

existence of such deficiency symptoms is important, in order to shorten convalescence in operative cases, or to prevent permanent disability

Ulcerative colitis, nontuberculous or nonamebic, offers an excellent example of a condition in which deficiency symptoms not infrequently occur Due to the persistent diarrhea with resulting improper absorption, loss of blood, anorexia, and occasional vomiting, there exists a background out of which almost any deficiency picture may be evolved It is important to recognize the fact already pointed out by Bargen, Larimore and others that the diets frequently prescribed may in themselves be so limited as to constitute an aggravating factor In such a disease there is an added factor of infection that undoubtedly contributes importantly either to the occurrence of the symptoms or prevents their proper treatment In the more severe cases which are extremely resistant to medical treatment in itself, ileostomy is at times indicated Such a procedure results in an immediate change in body physiology due to the increased loss of all intestinal contents through the new stoma Existing deficiencies are occasionally increased during this period at least unless properly guarded against, or until the processes of absorption are adjusted to the new situation In spite of ileostomy, however, the original disease may well continue to be active in the colon and because of secondary infection retard or prevent any amelioration of deficiency symptoms This, of course, is entirely analogous to the failure of otherwise adequate treatment in cases of pernicious anemia where there is coexistent focal infection In cases where the colon acts as a focus of infection it is occasionally advisable to perform a complete colectomy

In this communication 7 cases of ulcerative colitis will be presented to illustrate the points suggested above In each instance symptoms occurred during the course of the disease that could properly be classified as being due to dietary deficiency or to the presence of a serious persisting colonic infection

Case I.—W C, female, sixty-four years old Housewife Born in Massachusetts Typical gallstone attacks for years resulting in cholecys-

tectomy in 1919 Present illness began in 1921 with an attack of bloody diarrhea which recurred in 1923 1924 1925 1927 1928 1930 and 1931 With the exception of the original attack each recurrence apparently was initiated by fatigue or by severe emotional shock The recurrence of November 1928 persisted until April 1929 with loss of weight and a good deal of invalidism Toward the end of the attack she was troubled for about two months with a very sore tongue and many canker sores on the edges of the tongue and on the gums She mentioned at this time that she had frequent canker sores in the past associated with her diarrhea In 1924 and in 1930 and 1931 proctoscopy showed typical chronic ulcerative colitis

In the attack of 1930 she again complained very bitterly about her mouth symptoms At this time she showed numerous lesions on her gums and in the posterior pharynx as well as on the tip and edges of her tongue These lesions were small round superficial ulcerated areas with a yellowish white exudate and a grayish base. Cultures for monilia and other fungi were made on Sabouraud s medium but they were consistently negative Spirochetes were looked for but were not found It is of interest that during the diarrhea the diet had been very much limited by the patient and that with mild local treatment and with return to a well balanced diet the mouth and throat condition cleared up very rapidly

In June, 1931 because of another severe relapse she had an ileostomy performed since which time she has gained weight and strength has been able to eat a generous well balanced diet at all times and at no time has had further mouth symptoms until October 1932 At this time there was a prolapse of the ileostomy and just before and after the surgical repair of this her diet became limited At the same time a few of the mouth lesions reappeared disappearing rapidly just as soon as she returned to a more normal diet.

Case II.—J A male forty-one years old Insurance engineer Born in New Hampshire Past history essentially negative except for repair of an inguinal hernia twenty years ago and an operation for acute appendix two years before admission Bowel history had always been negative. Two years ago acute respiratory infection was followed three weeks later by an attack of watery diarrhea which was consisting of fifteen to eighteen movements in twenty four hours and nausea and vomiting for three weeks Not long after the appearance of the diarrhea he noticed ulcers on his tongue and in his throat which were very painful and persisted until the disappearance of the nausea and the vomiting During a period of nine weeks he lost 75 pounds and then went to a hospital where under proper treatment his movements diminished to a much smaller number At that time he was proctoscoped and was told that he had rectal polyps and ulcerative colitis. The mouth condition was described as consisting in only a small rounded reddened area with whitish crusts over it situated on the left side of the hard palate On leaving the hospital he continued to improve and had no further diarrhea until a year ago when there was a sudden appearance followed three weeks later by a return of the ulcerations in his mouth The mouth and tongue became extremely sore and it was difficult for him to eat The diarrhea con

tinued until his admission to the hospital and consisted entirely of loose watery movements with pus but no blood

Physical examination showed an undernourished man who was rather pale but was otherwise negative except for the condition in the mouth Inside the right cheek was a small grayish ulcerated lesion and two small punched out lesions about 2 cm in diameter on the under surface of the tongue. Cultures for fungi were negative and no spirochetes were found in the lesions A skin consultant said the condition was not due to tuberculosis or monilia Barium enema showed polypi throughout the entire course of the colon and proctoscopy confirmed the previous findings of polyps and ulcerative colitis Most of the polypi were typical adenomata and it was decided that proper treatment would consist of ileostomy with a subsequent colectomy Thorough anti amebic treatment had already been tried without any improvement although no amebae had ever been demonstrated

Ileostomy was done February, 1932, and was followed by a rapid improvement in his general condition, a striking gain in weight associated with an increased appetite and the complete disappearance of all the mouth lesions which have not recurred Colectomy is to be done in the near future

Comment—In the above 2 cases the tongue and mouth lesions constituted a very distressing, although not a serious, complication of the ulcerative colitis The lesions were essentially discrete, superficial grayish ulcers on the gums, cheeks, and the edges and tip of the tongue The tongue had not lost its papillae in either case, and in this respect did not resemble the tongue of pernicious anemia or sprue Achylia gastrica was not present in either case, and the blood was not at all suggestive of a primary hyperchromic anemia Search for Vincent's organisms or other spirochetes, or for fungi such as minilia, was unsuccessful Skin consultants considered the mouth lesions as due to the underlying nutritional disturbance In each instance, once the diarrhea had diminished and the patient was back on a well-balanced diet, recovery was rapid Recurrence was a feature and was always associated with a recurrence of the intestinal symptoms Ileostomy, with the resultant improvement in general condition, was associated with rapid remission of the mouth symptoms

Case III—E B, male, twenty-six years old Porter Past history essentially negative Present illness In 1927 following an attack of "grippe" he began to have diarrhea with five to seven bowel movements in twenty four hours associated with low abdominal cramps This condition continued

until he had to give up work and he remained in bed for several weeks with gradual improvement. In 1929 there was a recurrence with vomiting and diarrhea marked loss of weight and swelling of ankles A second recurrence later in the year with a final drop of weight from an original weight of 130 to 85 pounds At that time he noted soreness in the right forearm with soft tissue swelling and redness He was admitted to the hospital

Physical examination showed an emaciated young man with a dry red tongue. Heart and lungs were negative Abdomen was essentially negative except for some distention There was an area on the right forearm about 1 inch in diameter which was dark red slightly indurated with ill-defined edges and extremely tender A similar very tender area was present on the flexor surface of the right forearm and there was very definite limitation of motion of the right elbow There were also nodular subcutaneous swellings in the insertion of the right deltoid at the vertebral border of the right scapula and at the upper end of the right tibia They were tender and hot It was at first thought that the lesions were those of erythema nodosum but during the next few days they increased in size and it was decided that they were subcutaneous abscesses They were opened and drained Unfortunately cultures were not taken Proctoscopic picture showed typical chronic ulcerative colitis

Because of the extreme degree of malnutrition and the advanced ulcerative colitis ileostomy was decided upon and was performed without any unusual complications Within a short time after ileostomy the patient had begun to gain and there was a rapid healing of the skin lesions which had hitherto run a rather sluggish course. In the next year the patient gained 30 pounds and since that time has continued to improve. He has done heavy work during the past two years.

Comment—In Case III the peripheral complication was that of a very sluggish pustular skin infection The lesions were very painful, and were at first thought to be erythema nodosum, but subsequently proved to be pustular in nature Drainage gave relief If one could interpret such a condition as being metastatic, from the infection in the colon, it is surprising in view of the extremely serious condition of the patient that the organisms did not spread directly through the portal drainage area to the liver It is more probable that the lesions represented a skin infection due to a rather avirulent staphylococcus, to which the patient had no resistance Improvement of the patient's general condition was associated with complete clearing of the skin infection

Case IV—M B female sixty four years old Housewife. Born in Ireland. Past history Smallpox and typhoid as a child Jaundice at the

age of thirty-three, cause unknown Paroxysmal tachycardia in the last few years For years the patient had eaten little or no meat or citrus fruits

Present Illness—One and one-half years ago the patient had an acute attack of diarrhea with blood without preceding symptoms She had very frequent bowel movements for a month and was confined to her bed Since that time she was up and around the house doing her housework but was obviously in poor condition to do so Her appetite had decreased but there was said to be little loss of weight At the end of a year her bowel movements had fallen to between two and five in twenty-four hours The bleeding had increased but there was no pain

Physical Examination—A somewhat emaciated old woman with a very shiny smooth red tongue, there were no ulcerations Examination of the heart showed typical arteriosclerotic and hypertensive heart disease without failure. x-Rays Barium enema showed diverticula and a saw-tooth irregularity of the sigmoid Gallstones were also visualized Proctoscopy showed a narrowed rectum, the mucous membrane of which was scarred and contained small superficial ulcers that bled readily Search for amebae was unavailing and the stools were typical of chronic ulcerative colitis with large amounts of blood and pus Failure to improve on fairly prolonged medical treatment resulted in a decision to resort to ileostomy This decision was arrived at in view of loss of weight and anemia in spite of careful dietary and other measures Following the ileostomy her tongue and mouth condition became worse for about two weeks and the mouth was so sore that it was impossible for the patient to take any hot drinks Twelve days after ileostomy a small marginal ulcer appeared on the left cornea and persisted for about two weeks As soon as the patient had become accommodated to the ileostomy, and food intake was satisfactory, the tongue condition and the corneal ulceration cleared up rapidly The patient gained in weight and returned home There has been no recurrence of mouth or eye symptoms and she is at present doing her own housework

Case V—S M , male, thirty-seven years old Truck driver Born in Massachusetts Past history essentially negative except for the existence of a slight pustular skin eruption of about eight years' duration Present illness November, 1930, insidious onset of diarrhea, six to eight movements in twenty four hours, gradually improving until actually constipated three months, but as a result of castor oil the diarrhea returned and became bloody In six months' time he lost 75 pounds in weight Appetite good

Physical examination on admission showed him to be undernourished The skin showed a pustular rash over the face and thorax There were red papules and some pustules on the mucous membranes of the pharynx. There was a decubitus ulcer over the sacrum Small amount of fluid in the left knee No peripheral edema Proctoscopy Mucosa shows frequent large linear ulcers with exudate Stools show blood and pus, no amebae After a month of medical treatment and failure to gain, an ileostomy was done because of persistence of elevated temperature, bloody diarrhea, and rapid loss of weight Convalescence was uneventful and he did well for a few weeks, then had an ischiorectal abscess which ruptured This was drained two months after

the first admission and at the same time an abscess on each hip which had appeared in the preceding few weeks was opened and drained Five months later the patient was admitted for the third time He had gained 45 pounds in weight his appetite was good but he continued to have seven urgent rectal movements in twenty four hours His diet had been somewhat limited especially in protein content. At this time he presented a rather serious ulceration of the right cornea Skin was very dry with scales papules pustules and scabs and his tongue was extremely sore Distribution of the skin eruption was fairly general There were physical signs of low grade chronic bronchitis.

Proctoscopy showed a very much scarred contracted rectum and the mucous membrane was hemorrhagic. The patient had recently begun to lose weight again Temperature was elevated He was unable to work and because of these considerations and the skin and eye condition it was decided to perform a colectomy This was done at the end of October 1931 and during an uneventful convalescence his condition improved very rapidly The corneal ulcer healed and the skin condition improved tremendously in a few weeks March 1932 he had gained 23 pounds and had only small traces of his skin condition September 1932 he was back to his original weight felt well was working hard and had had no recurrent skin eye, or tongue manifestations

Comment.—In both of the above cases, the patients suffered from tongue disturbances and from corneal ulcers The tongue in Case IV was similar to that seen in pernicious anemia or sprue and while extremely sore cleared up completely with the improvement of the underlying colonic disturbance While the patient was recovering from the ileostomy, however, the extreme soreness of the mouth made proper dietary measures difficult to carry out. The corneal ulceration was also not serious but caused marked discomfort and persisted for about three weeks, clearing up only as the general nutrition of the patient improved In the second case, the corneal ulceration was the symptom that eventually caused the patient to return to the hospital after ileostomy Continued loss of weight, and a persistence of bloody rectal movements, associated with a very marked increase in a skin condition of long standing, were of more serious import and combined to force a final decision in favor of colectomy During the patient's last period of hospitalization there were also rather distressing tongue symptoms Colectomy was performed without any serious complications and the very rapid improvement of the general condition and

of all the above peripheral manifestations was an extremely striking occurrence It seemed logical to assume that the latter were intimately associated with the underlying colonic sepsis and the malnutrition

Case VI.—I S , female, thirty-eight years old Housewife Born in Massachusetts Past history uneventful except for an attack of diarrhea said to be due to paratyphoid infection eighteen years previously Present illness Sudden onset three weeks after delivery of normal child, third pregnancy, in January, 1932 Movements gradually increased and were associated with high temperature Two weeks later blood appeared and her condition gradually became more serious One month after onset, tongue was very dry, edema of shins and ankles, and knee jerks were present One month later condition had not improved, patient had lost a great deal of weight and was admitted to the hospital

On admission she showed emaciation, edema of the feet and ankles, very dry sore tongue, extreme pallor, and a proctoscopic examination revealing polypi and some ulcerations Red count 2,980,000, hemoglobin 60 Serum protein 4 6 mg per 100 cc Patient went downhill rapidly and ileostomy was performed one week later following transfusion Convalescence stormy Rectovaginal fistula one week after operation After ileostomy the patient's condition was critical for a month, complicated by marked edema of the legs, a very sore nonulcerated tongue, corneal ulcers, and gradual development of a peripheral neuritis with a loss of knee and ankle jerks The latter increased until there was a marked foot drop and an absence of position sense With transfusions and a gradual increase in food intake, she slowly improved and was discharged from the hospital about two months after her admission At that time her tongue was normal and her corneal ulcers had disappeared The edema was nearly gone Five months later after a gradual continuous improvement she had returned to her original weight, was doing a little housework, and felt well There were still evidences of a mild peripheral neuritis, but the condition had improved tremendously

Case VII —E M , male, twenty-six years old Store manager Past history unimportant Present illness Three years before admission to hospital acute onset of diarrhea, fever, nausea, vomiting, all of short duration Recurrence in 1931 In two months he lost a large amount of weight and was treated for ulcerative colitis at another hospital with some improvement A subsequent recurrence, however, was followed by an ileostomy following which his progress was unsatisfactory and he eventually noted tachycardia, sore mouth, and numbness and tingling and weakness in the arms and legs At the time a diagnosis of beriberi was made and shortly after he had what seemed to be an acute attack of heart failure with pulse of 160 He was transferred to the Massachusetts General Hospital at which time he was completely disoriented for several days, refusing to talk or giving only irrelevant answers The tongue was smooth, sore, knee jerks, and

ankle jerks were not obtained and he had tenderness over the nerve trunks in the feet and legs He had lost a good deal of weight

He was fed by nasal tube being given a high caloric mixture with large amounts of yeast and cod liver oil In eight days there was marked improvement in his mental condition and in three weeks he was able to be up and around in a wheel chair The signs of peripheral neuritis persisted but the tongue soreness had disappeared Four months later after he had been on a careful diet at home, he still was having bloody diarrhea by rectum and was being bothered by a pustular skin eruption The fingers and toes were still numb and there was toe drop On second admission to the hospital he showed better nutrition than previously but there was a pustulous skin eruption with general distribution atrophy of both legs and definite weakness of all muscle groups Foot drop Absent knee jerks and ankle jerks Numbness of the feet and loss of vibration sense on the right He was obviously not improving and it was felt that colectomy was advisable. This was done in March 1932 and was followed by a normal convalescence From then on he has improved steadily except for local sepsis around the rectum which has had to be drained The total gain in weight has been about 40 pounds in six months. Before and after the ileostomy the tongue was very sore and at one time there were said to be white spots on the edge of the tongue. During the period of so-called beriberi his feet and legs were swollen There were no corneal ulcers. At present with the exception of a little remnant of pustulous skin eruption on his face and a slight toe drop he is essentially a normal individual During the summer he walked and swam and is fairly active at present

Comment—In the last 2 patients the effect of dietary deficiency was striking Mrs S had nutritional edema, as evidenced by her very low serum protein, and a peripheral neuritis These conditions undoubtedly were due to actual lack of sufficient protein and of the antineuritic vitamin Ileostomy temporarily increased the nutritional edema and may have been the final responsible factor in the production of peripheral neuritis, inasmuch as the malnutrition was undoubtedly aggravated during the three or four weeks following her operation The appearance of corneal ulcers may have been due to nutritional disturbances or associated with the colonic infection

In the case of Mr M the situation was similar to that of the preceding patient, but was more pronounced Again the skin condition may well have been fundamentally associated with the colonic sepsis On the other hand, the appearance of cardiac failure, associated with nutritional edema and a very severe peripheral neuritis and mental disturbances suggests a dietary deficiency of a nature like that found in beriberi In

this case at least the peripheral complications were extremely important from the point of view of prognosis, but with proper dietary care a marked improvement was possible The effect of sepsis on the treatment of deficiency conditions was well illustrated here, however, inasmuch as what would otherwise have been extremely adequate dietary therapy was not sufficient to permit a real cure of the edema and the neuritis Only after colectomy was it possible to obtain satisfactory results

The above cases have been presented to illustrate the development of certain peripheral manifestations of dietary deficiency and sepsis, as they may occur in ulcerative colitis Such symptoms are frequently seen in other medical and surgical conditions, and are mentioned in connection with this specific disease only for the purpose of suggesting the mechanism favoring their appearance Ileostomy, while at times a necessary surgical procedure in the proper treatment of ulcerative colitis, is a measure which may aggravate any underlying dietary deficiency, and should be undertaken only with a thorough understanding of necessary therapeutic measures to combat such effects Frequently a well-balanced diet provides adequate therapy for a condition of undernutrition An adequate protein intake should be assured, however, and in a condition such as ulcerative colitis where the normal processes of absorption are interfered with, it is advisable at times to make use of concentrated preparations which are high in vitamin content The rôle of residual infection must be appreciated as regards its inhibitory influence on otherwise successful therapeutic measures, and additional steps at times must be taken even though they involve a procedure as serious as colectomy, in order to effect a complete cure

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THE DIFFERENTIAL DIAGNOSIS OF ACUTE ARTHRITIS

ONE of the most perplexing problems confronting the physician is the accurate diagnosis of arthritis As an aid in discriminating between cases more carefully, an attempt should be made to discover the etiologic agents, and this can only be done by a consideration of all the factors in a given case We will present 4 patients who illustrate how arthritis may be one manifestation of a more generalized disease, and although in each case the arthritis was the complaint for which the patient sought advice, later it was found to be merely the presenting and not the primary condition

Case I. A Patient with Subacute Polyarthritis, Painful Lymphadenopathy, Maculopapular Syphilides, and a Positive Wassermann Test Shows Prompt Improvement of Arthritis Following Antisyphilitic Treatment—An Italian laborer sixty-eight years of age, was admitted to the Boston City Hospital complaining of joint pain He had been symptom free until two months before entry when he experienced sensations of chilliness, first at night then also during the day which were accompanied by coryza increased lacrimation and a cough productive of a moderate amount of mucopurulent sputum These symptoms persisted for approximately one month after which they were of little consequence. Later swelling tenderness, and local increase in heat appeared to involve the knees and within a few days the ankles. During the three weeks immediately preceding entry there had been pain on motion and stiffness of the hips spine shoulders elbows wrists and fingers in addition to the knees and ankles which became so severe that he was confined to bed During his illness he had lost weight and slept poorly

The family history was irrelevant He had been married for thirty six years and his wife had had seven pregnancies Five children were living and

well One child died at three months of age, cause unknown, and there had been one miscarriage His family lived in Italy, although he had been in this country for twenty-one years Since his immigration his sexual habits had been highly promiscuous Early in life alcohol had been used in excess

The past history was also relatively unimportant He denied all illnesses except measles as a child, and malaria at the age of fourteen He denied gonorrhea and syphilis by name and symptoms He had a bilateral inguinal adenitis with subsequent suppuration, and incision at the age of seventeen

Physical examination showed a man, well-developed and well-nourished with a temperature of 100 F , pulse 80 per minute, respirations 22 per minute, and a blood pressure of 165 mm Hg systolic and 80 mm Hg diastolic His complaint was of painful aching joints which became more severe on exertion The skin was soft, warm, and moist There was a maculopapular light rose-colored generalized eruption Pruritus was present The mucous membranes were normal in appearance The lymph nodes were everywhere palpable, enlarged, and tender The joints of all extremities, the sternoclavicular articulation and the spine, were exquisitely tender and painful on motion The knees were hot and swollen, and showed evidence of an increase in intracapsular fluid but were not red There was slight edema of the feet An arcus senilis was present, and the ocular fundi showed vascular changes There was marked oral sepsis The pharynx was injected The tonsils were small, and showed some follicular exudate There were a few moist râles at the bases of both lungs The heart was enlarged to the left The cardiac rate was slow but irregular due to frequent extrasystolic beats The heart sounds were normal A soft systolic blowing murmur was evident over the apex The walls of the peripheral arteries were thickened and somewhat tortuous The prostate was slightly tender, moderately enlarged, and of boggy consistency The remainder of the physical examination was negative

The urine examination was negative except for an occasional leukocyte

The hemoglobin was 70 per cent (Sahli), the red blood cells 4,300,000 per cubic millimeter, and the white blood cells ranged between 6000 and 9800 per cubic millimeter The differential count of the latter was polymorphonuclear leukocytes 69 per cent, lymphocytes 23 per cent, mononuclears 8 per cent The smear showed the red blood cells to vary moderately in size and shape and to be slightly pale The blood Kahn and Wassermann reactions were positive on two occasions

The prostatic fluid showed a few leukocytes but no gonococci

An x-ray examination of the chest revealed the lung fields to be clear The aorta was widened suggesting aortitis, and the heart was enlarged to the left The knees, elbows, and hands showed hypertrophic (degenerative) arthritis

As a result of the above findings the diagnosis of syphilitic arthritis was made, and the patient received eight injections totalling 2 95 Gm of neoarsphenamine with the resultant complete disappearance of the rash, lymph node enlargement, and subsidence of joint pain The patient was discharged from the hospital after six weeks when he was essentially free of symptoms

It is important to recognize syphilis as a cause of acute or subacute arthritis because immediate and thorough treatment with antisyphilitic remedies is followed by complete recovery, as occurred in this case

Syphilitic arthritis has been studied recently by Chesney Kemp, and Resnik,[1] Chesney, Kemp, and Baetjer [2] and Kling In 1923, Chesney, Kemp, and Resnik reported 2 most interesting cases of acute syphilitic arthritis and demonstrated for the first time *Treponoma pallida* in the joint fluid These cases were characterized by *acute polyarthritis, painful lymphadenopathy a skin eruption*, and *eosinophilia* Following antisyphilitic treatment all of these features disappeared Later Chesney[3] studied other cases and called attention to the fact that both acute and subacute forms of arthritis are due to syphilis Kling emphasized that syphilitic arthritis can imitate any form of joint disease and should be considered as an etiologic agent in all obscure cases of arthritis In most cases the blood Wassermann reaction is positive, but in one case reported by Chesney the joint fluid yielded a positive Wassermann reaction and the blood Wassermann reaction was negative It is important, therefore, to study, if possible, the joint fluid, as well as the blood, in these cases when it can be obtained It usually shows an increase in cells, the lymphocytes and monocytes predominating

For a complete and exhaustive discussion of the older literature dealing with syphilitic arthritis Schlesinger's[4] monograph on the subject is available

Case II. A Patient with a Carcinoma of the Lung Admitted to the Hospital with Symptoms of Polyarthritis—A longshoreman forty nine years of age, entered the Boston City Hospital complaining of headache, nervousness and painful joints Four months before entry he had received a blow over the right parietal region which was followed by unconsciousness for a few minutes. Later headache and dizziness occurred but these symptoms gradually subsided over a period of ten weeks. Two and a half months before entry his knees and ankles were stiff painful and swollen upon arising this was followed within a week by swelling pain and stiffness of the fingers. The knees ankles and fingers remained swollen painful and stiff for two months. The pain had been severe enough to inhibit sleep The joint symptoms had been somewhat relieved by exercise Mild night sweats were

frequent Twenty to 25 pounds weight was lost during the course of the illness

The family history was irrelevant

The past history was entirely negative except for measles at the age of seven years, gonorrheal urethritis at the age of thirty, and an excessive use of alcohol over a number of years

Physical examination showed a well-developed, poorly nourished white man, who appeared somewhat listless and in no acute distress His temperature was 100 F , pulse 92, and respirations 20, and the blood pressure was 110 mm Hg systolic and 50 mm Hg diastolic Small, firm, discreet lymph nodes were found in the cervical, inguinal, and left epitrochlear regions The knees were swollen and painful, and gave evidence of a considerable increase in the intracapsular fluid The ankles were painful and showed much soft tissue swelling The elbows were held in semiflexion Motion was difficult in spite of the little pain elicited There was definite clubbing of the fingers with red, swollen nail beds The scar in the right parietal region was well healed and clean, but slightly tender on pressure The ocular fundi showed slight vascular retinitis All teeth but one were missing The breath was foul The percussion note was somewhat impaired throughout the right chest, the breath sounds were distant with slight prolongation of the expiratory phase, and fine râles which persisted after coughing were heard over the right chest The area of cardiac dulness was increased, the heart sounds were distant and of poor quality, and a faint systolic blowing murmur was heard over the precordium The peripheral arteries were sclerosed and tortuous The pulses were equal and regular

The urine examinations were normal

The hemoglobin and red blood cells fell from 92 per cent (S) and 4,400,000 per cubic millimeter on admission to 60 per cent (S) and 3,500,000 per cubic millimeter respectively in the course of two months The white blood cell count varied between 4300 and 13,900 The blood Kahn and Wassermann reactions were positive on three examinations

The sputum was negative for tubercle bacilli on several examinations

x-Ray studies showed extensive periosteal proliferation of the bones of all extremities and the spine and a rounded mass in the lower lobe of the right lung about 2 inches in diameter, which gradually increased in size in spite of therapeutic measures

Neoarsphenamine, 3 5 Gm in ten injections over a period of six weeks, and potassium iodide in moderate dosage did not lead to any improvement Deep x-ray therapy failed to alter the growth of the mass An attempt to produce a pneumothorax was unsuccessful The mass in the right lung continued to increase in size, the anemia increased, loss of weight continued, and the joint symptoms persisted The patient finally developed cyanosis, a nonproductive cough, and pain in the chest He died two and a half months after admission

The autopsy revealed an adenocarcinoma of the right lung with metastases to the lymph nodes of the mediastinum, the liver, and the bone marrow There was a moderate degree of arteriosclerosis A small amount of fluid was found in the right pleural cavity and the peritoneal cavity The

liver spleen kidneys and stomach showed chronic passive congestion There was a moderate pulmonary edema and congestion The pleura pericardium and peritoneum were covered in certain areas by old fibrous adhesions and plaques. The joints were not examined

This patient illustrates how a small carcinoma of the lung may be disguised as an arthritis Bone lesions in carcinoma of the lung are of three kinds, metastatic lesions of the bone marrow invading the cortex of the bone, periosteal metastases and periostitis associated with clubbed fingers, the so-called 'hypertrophic pulmonary osteo-arthropathy" In this patient there were metastases in the marrow cavities and a definite hypertrophic pulmonary osteo arthropathy was demonstrated by roentgen ray examination Whether or not there were periosteal metastases is not known, as the periosteal lesions were not examined postmortem

Hypertrophic osteo arthropathy as a complication of lung tumors has been discussed by Locke,[4] Weinberger,[5] and others In one case described in detail by Locke, there were periosteal metastases as well In a case reported by Thomas, Hirsch, and Blaine[6] there were extensive periosteal metastases without clubbing of the fingers

Of considerable interest is the pain and swelling of the joints This probably resulted from the inflammation of the periosteum within the capsule of the joint cavity, as one could detect pain and swelling of the joints, and trace the pain along the periosteum of the involved bones In some cases, the joints, particularly the knees, are swollen and contain an excessive amount of fluid In most cases, however, while the pains may be referred to the different joints by the patients, there are no demonstrable lesions of the joints themselves Fraenkel[7] did not find any characteristic gross or microscopical changes in the joints of 6 cases which he examined anatomically, and Crump[8] observed no gross changes in the joints, but found areas of round-cell infiltration in the capsule of the knee joints when they were examined microscopically The conditions to be considered in differential diagnosis, since they produce periostitis as well as joint inflammation, are syphilis and gonorrhea The former

produces changes in the periosteum much more frequently than the latter Neither produces clubbing of the fingers

Case III A Male Patient with Hemophilia Enters the Hospital with Symptoms of an Arthritis of the Right Ankle Examination Reveals Chronic Changes in Ankle Joints —A white man, thirty-six years of age, was admitted to the Boston City Hospital, complaining of pain and swelling in the right ankle of three weeks' duration He denied any knowledge of preceding trauma Since early childhood he had been considered a hemophiliac There has been frequent copious epistaxis, an intermittent hemorrhage of two weeks' duration following the extraction of a tooth, and bleeding for a week following a laceration of the scalp He had never had hematuria or melena Both ankles, the left more frequently than the right, had for years, with and without obvious preceding known trauma, become swollen and painful and occasionally the skin had become discolored with the subsidence of the pain and swelling The most recent involvement was the right ankle six months previously The left and right knee, ten and six years ago respectively, became markedly swollen and painful following mild trauma Six years ago as a result of a fall, a large mass appeared over the left ilium associated with severe pain on motion of the left hip and was followed by marked discoloration of the overlying skin Both wrists had been moderately swollen and painful following slight trauma repeatedly for the past fifteen years The right elbow had been frequently the site of swelling and pain following slight trauma for the past twenty-four years The left elbow had been also similarly involved but less frequently and less severely

The joints had remained stiff, and there had been occasionally crepitation on motion for about one month after the subsidence of the acute symptoms but it was not permanent

The patient has two brothers, aged forty-five and twenty-seven years, who have hemophilia, both of whom have had involvement of their joints One brother aged thirty-three years is living and well Two other brothers died in infancy as a result of profuse hemorrhages Two sisters, living and well, have had no male children The patient knows nothing of the occurrence of hemophilia in members of previous generations of his family

Physical examination revealed a well-developed but poorly nourished white man who seemed to be mentally deficient The teeth showed numerous cavities The right ankle was moderately swollen, and the skin over it was of a brownish color Passive and active motion of the right ankle was limited The left ankle was also slightly swollen and there was slight limitation in motion both in flexion and extension Both elbow joints were enlarged The knees and wrists showed no abnormalities The remainder of the physical examination was negative

The hemoglobin was 82 per cent (S), the red blood cells 4,870,000 per cubic millimeter, and the white blood cells 6850 per cubic millimeter The differential count was polymorphonuclear leukocytes 69 per cent, polymorphonuclear eosinophils 1 per cent, lymphocytes 23 per cent, and mononuclears 23 per cent The blood platelets were 550,000 per cubic millimeter The Kahn reaction was negative The coagulation time of 1 cc of venous

blood in a test tube of 0 9 cm diameter has been between one hour and two hours and fifteen minutes (Lee) on repeated examinations

The urine examinations were negative. The spinal fluid was normal in all respects.

Upon *x* ray examination the *tarsals knees elbows* and *hips* were found to be negative. Both ankles showed bone reaction and cystic degeneration in the lower tibia (Fig 170) The *x* ray examination of the chest revealed an old tuberculous lesion at the left apex and an old pleuritis of the left base

This patient illustrates one of the most common and most distressing complications or symptoms of hemophilia, namely, multiple hemorrhages into the joints Many of the patients with hemophilia sooner or later have such occurrences They usually follow known trauma, but in some cases it may be so slight that a history of violence is not obtained One boy we have observed recently developed hemorrhage into his knee and ankle joints following such exercise as walking The movements of the joints caused enough trauma to the synovial membrane, which is normally very vascular, to bleed extensively

It is very important to recognize this condition, and under no circumstances should the joint be manipulated or opened If the hemorrhage is a large one, an acute pyogenic arthritis may be suspected by the presence of the local signs, fever, and moderate leukocytosis, but a history of bleeding in a boy with a prolonged coagulation time of the blood should make the diagnosis a relatively easy one

The lesions observed may be divided into two main types—acute hemarthrosis, and chronic arthritis resulting from repeated trauma and hemorrhage In most cases both processes are observed in the same patient, if he is seen repeatedly

In the case of an acute hemarthrosis which is most common in the knees, ankles, hips, and elbows, the swelling may occur with great rapidity As a rule, a history of injury is elicited, but it may be so slight that the hemorrhage into the joint appears to be spontaneous Simple pressure on the elbow joint is often sufficient The pain and disability will depend upon the degree of swelling and pressure within the joint There is usually some fever and moderate leukocytosis If the part is put at rest the swelling usually subsides within a week or ten days

In most cases the joints return to normal after the first hemorrhage, but unfortunately the bleeding is frequently repeated It is in these cases that chronic changes in the joints are observed They are the results of repeated trauma and hemorrhages, and can best be discussed by considering changes in the synovia, the cartilage, and the bone respectively

Fig 170 —x-Ray of right ankle joint showing cysts in the lower end of the tibia

Key[9] has recently discussed the pathologic alterations of the synovia and reviewed the literature on the alterations of the cartilage and bone The synovial changes can be summarized as follows As a result of the hemorrhages a hyperplasia of the synovia occurs with an increase in the fibrous tissue of the subsynovial layer This tissue becomes infiltrated with macro-

phages, and contains large amounts of iron pigment resulting from the broken-down hemoglobin Upon repeated hemorrhages the synovia continues to hypertrophy and forms numerous villi, and a layer of dense fibrous connective tissue in the subsynovial tissue, with a decrease in the size of the synovial cavity In such cases there is a tendency to fibrous ankylosis of the joint This fibrous ankylosis limits the motion of the joint and inhibits the resorption of blood from the joint cavity

In many cases there is very little destruction of cartilage except at the margins It is stated that in other areas there may be an irregular destruction of the cartilage which does not coincide with pressure areas in the joints The mechanism for this type of destruction is not clear, but it is thought to be the result of subchondral hemorrhage.

The common changes in the bone are cavities in the cancellous portion (Fig 170) The origin is not clear but they probably result from intra-osseous hemorrhage, which produces an area of aseptic inflammation, with subsequent absorption of bone

The condition revealed by an x ray examination of a joint in a hemophilic patient depends upon the stage of the process The periarticular tissues may show increased density due to the deposition of old blood pigment, irregularity of the joint margins, a decrease in the size of the joint cavity, and cavities in the bones

The diseases which must be differentiated from these conditions are acute pyogenic arthritis and tuberculosis The history is of great importance The occurrence of the condition in a boy, and the presence of a prolonged coagulation time of the blood, will establish the diagnosis

Case IV **A Patient with Polyarthritis and Acute Nephritis Following an Attack of Acute Follicular Tonsillitis** —A policeman twenty-eight years of age was admitted to the Boston City Hospital complaining of pain in the joints Six weeks prior to entry he was confined to bed for several days with an attack of acute tonsillitis He was given diphtheria antitoxin but later the throat cultures were reported as negative for Klebs-Loeffler bacilli Ten days after the serum therapy he had painful joints and definite lymph node enlargement which lasted from three to four days Eighteen days before entry he complained of constant aching pains in both lumbar regions with

tenderness in the costovertebral angles At the same time he experienced burning on micturition and frequency There was no obvious gross hematuria nor pyuria Ten days before entry the right elbow became swollen, tender, and painful which was followed closely by similar involvement of the left elbow, the knees, the ankles, and the thumbs The patient perspired freely and slept poorly Methyl salicylates locally, and sodium salicylate and sodium bicarbonate by mouth, afforded no appreciable relief

The family history was noncontributory The patient had been married for four years His wife had 2 children, both of whom were living and well There were no other pregnancies His habits had always been good

The past history was entirely negative except for measles at the age of five, and Vincent's angina at the age of seventeen Sore throats had been quite rare

Upon physical examination the patient was found to be a well-developed and well-nourished white man in no apparent distress but perspiring freely His temperature was 99 F , pulse rate 100 per minute, respiration 20 per minute and the blood pressure 150 mm Hg systolic and 100 mm Hg diastolic The skin was pale, warm, and moist The mucous membranes were moderately pale The cervical lymph nodes were enlarged, soft, and tender No other nodes were palpable except the inguinal ones which were small, discrete, and nontender There was tenderness and soft tissue swelling, but no redness nor locally increased heat around the knees, elbows, and thenar eminences Examination of the ocular fundi revealed normal eyegrounds There was a slight pyorrhea The tonsils were red, cryptic, and small The pharynx was moderately injected and showed hypertrophy of the lymphoid tissue The lungs were clear to percussion and auscultation The heart sounds were normal No murmurs were detected The pulses were equal, regular, and of good volume The vessel walls were smooth and easily compressible There was slight costovertebral tenderness No edema was demonstrable

The urine consistently showed albumen, casts, red blood cells, and leukocytes The phenolsulphonphthalein test showed 26 per cent excretion of the dye in two hours on admission and 30 per cent in two hours one month later The specific gravity of the urine varied between 1 008 and 1 018

An examination of the blood showed a hemoglobin of 75 per cent (S) and red blood cells 4,150 000 per cubic millimeter The leukocyte count was 28,200 per cubic millimeter on admission, which fell promptly to remain between 12,000 and 14,000 per cubic millimeter The differential count was polymorphonuclear leukocytes 80 per cent, eosinophils 2 per cent, lymphocytes 12 per cent, monocytes 6 per cent The red blood cells on smear varied in size and shape and were of a moderate pallor The nonprotein nitrogen of the blood was 21 mg per 100 cc on several examinations The Kahn and Wassermann reactions of the blood were negative

The temperature reached 100 F for two days after entry and remained normal thereafter The extraction of an abscessed tooth, a tonsillectomy and adenoidectomy were not followed by a further elevation in temperature nor an exacerbation of symptoms or signs of acute nephritis The joint symptoms improved satisfactorily and he was discharged after six weeks

In summary, this patient presented two of the commonest complications following an acute streptococcal infection of the lymphadenoid tissue of the throat, namely acute nephritis and acute arthritis He recovered completely from both conditions the arthritis disappearing before the nephritis

When one encounters an acute arthritis following acute follicular tonsillitis or scarlet fever, four possibilities immediately come to mind First, is it an attack of acute rheumatic fever? Secondly, is it a metastatic arthritis from a thrombophlebitis of the tonsillar veins (postanginose sepsis)? Thirdly is it the so-called post scarlatinal "toxic" arthritis following acute streptococcal infection? Lastly, if the patient has received serum, has serum sickness with joint symptoms resulted? In this case it was felt that the condition was one of the third group, because none of the characteristic lesions of acute rheumatic fever could be demonstrated, that is, subcutaneous fibroid nodules, electrocardiographic changes or evidence of pericarditis As the clinical course was not similar to a metastatic arthritis, the second group was excluded

In recent years, there has been a tendency to assume that all cases of acute polyarthritis occurring after acute streptococcal infections are examples of acute rheumatic fever, largely because rheumatic fever commonly occurs after such infections, and because patients who have had an earlier attack of acute rheumatic fever prior to an attack of scarlet fever or follicular tonsillitis often have a recurrence It also has been emphasized that patients who die of scarlet fever frequently show anatomical changes in the heart muscle resembling in some respects at least those found in rheumatic heart disease Until we know more about arthritis following scarlet fever, it seems wise to make the diagnosis of rheumatic fever only in the cases in which it is possible to detect cardiac lesions either by physical examination, by electrocardiographic changes or by finding the characteristic subcutaneous fibroid nodules

The arthritis associated with sepsis following tonsillitis is a true metastatic lesion The primary focus is a thrombophlebitis of the tonsillar or ascending palatine veins These

cases are usually due to hemolytic or anaeroebic streptococcal infection and have been studied particularly be Fraenkel,[10] Lenhartz,[11] Reye,[12] and others The characteristic features of this type of sepsis are the onset of chills, fever, and sweats following an acute angina The local lesion in the throat may show signs of improvement as the patient's general condition becomes worse One usually finds some swelling and tenderness of the lymph nodes of the neck, and if the infection extends into the internal jugular veins, localized pain and tenderness over the veins may be present Suppurative metastases to the lungs and joints are common, and the blood cultures are usually positive, particularly if anaeroebic cultures are made

The so-called "toxic" arthritis following scarlet fever is observed in about 6 per cent of the cases (Jochmann) It is slightly more common in adults than in children and is usually accompanied by fever It is observed most commonly in the second half of the first week but may not appear until the second or third week The blood and synovial fluid are usually sterile This is in striking contrast to the purulent variety of polyarthritis which occasionally follows scarlet fever, because in these cases there is usually a positive blood culture As a rule, the joint cavities do not contain large amounts of fluid but when it is obtained it has the characteristics of a serous exudate Alexander[13] and McClure[14] have pointed out that both arthritis and myositis are common, as in our patient The most obvious feature is pain and elevation of local temperature There may be very little tenderness, redness or swelling of the joints In mild cases there may be an absence of fever, and in some the joint pains appear with an elevation of the temperature above normal In others, fever may be present for twenty-four to forty-eight hours before the appearance of the arthritis The joint pains may last from three to ten days, but McClure has observed some cases in which the pain persisted for as long as fifty-five days It is somewhat more common to observe involvement of the small joints early in the course of the disease and the large joints later The joints of the fingers, knees, elbows, shoulders, and ankles are most commonly involved

It is important, then, in any case of arthritis following streptococcal infection, to differentiate the condition insofar as it is possible from acute rheumatic fever and septic arthritis

From these 4 cases it is seen that pains in the joints may be the presenting symptom of a variety of diseases and only by a consideration of all the facts in the given case can the complete diagnosis be made

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Both Alexander and McClure state that salicylates do not seem to affect the course of the arthritis In our patient some symptomatic relief of the joint pains was observed following this type of therapy As a rule, the prognosis is good and recovery is complete without joint damage or recurrence

In the patients who have received antistaphylococcal serum it is necessary to differentiate the arthralgia of serum sickness from this condition In some cases it is extremely difficult because the two conditions are very similar and many of the features characteristic of serum sickness may be reproduced in patients with postscarlatinal complications who have not received serum

It is important, then, in any case of arthritis following streptococcal infection, to differentiate the condition insofar as it is possible from acute rheumatic fever and a septic arthritis

From these 4 cases it is seen that pains in the joints may be the presenting symptom of a variety of diseases, and only by a consideration of all the facts in the given case can the complete diagnosis be made

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PLASMA PROTEIN DEFICIENCY IN PATIENTS WITH CARDIAC EDEMA

EDEMA may be broadly classified into two groups cardiac and noncardiac. The two types have very different causes and required different forms of therapy The production of cardiac edema is usually due to increased pressure in the capillaries transmitted back through the veins from an inefficient heart As a result of this increased capillary pressure the passage of fluid from the blood into the tissues is helped and the passage back into the blood hindered In contrast to the purely mechanical production of cardiac edema the edema of chronic nephritis and certain other conditions is closely associated with a reduction of the proteins of the plasma These proteins form the chief portion of the colloids of the blood plasma to which the capillary walls are normally almost impermeable. An osmotic pressure is thus created tending to draw fluids from the tissues into the blood vessels The hydrostatic and osmotic pressures are in opposition throughout the length of the capillaries Under normal circumstances the hydrostatic effect is greater at the arterial end of the capillary loops with the result that fluid passes out of the vessels, and the osmotic effect predominates at the venous side of the loops which draws the fluid back into the blood stream, so that an equilibrium is established In conditions in which there is a marked depletion of plasma proteins the passage of fluid into the tissues occurs with greater ease than its return to the blood and edema results

The normal level of total proteins of the blood plasma is from 6.3 to 8 Gm. per 100 cc with an average of about 7 Gm [1]

The critical level for the plasma proteins at which edema appears is about 5 to 5 5 Gm per 100 cc These figures are for analyses for protein carried out on heparinized blood by the Kjeldahl method When the analyses are made on oxalated blood, as was the case with the results reported here, the figures are 0 3 to 0 4 Gm lower than those stated above

The lowering of the plasma proteins in the conditions discussed in this Clinic is chiefly, if not entirely, at the expense of the albumin fraction of the plasma proteins Determination of changes in the level of the plasma albumin provides a closer correlation with the tendency for the occurrence of edema than do estimations of the total plasma proteins However, the simplicity in the determination of the total proteins as compared to the albumin fraction, makes this test one which is more practical and is adequate for routine clinical purposes

The treatment of the two types of edema is, of course, radically different Where the edema is due to increased hydrostatic pressure as a result of heart failure, proper therapy is chiefly directed toward restoring the normal cardiac function by rest and digitalis When low plasma proteins are responsible for the edematous condition, then the therapeutic attack should be aimed at restoring these proteins to a normal level Specific diuretic drugs and measures are often of value in the symptomatic treatment of both types of edema

As previously stated the chief and often the only cause of cardiac edema is the increased mechanical back pressure in the veins and capillaries resulting from a failing heart However, in a certain number of patients with congestive heart failure, complicating factors arise which tend to lower the plasma proteins, and this reduction of the proteins aggravates the already existing edema or causes it to persist in spite of the usual cardiac treatment It is not widely appreciated that this may be so, although it has been emphasized previously, notably by Payne and Peters[2] and by Peters and Van Slyke,[1] and since proper therapy will often accomplish much to raise the proteins to a proper level with consequent clinical improvement, it is the purpose of this communication to stress this element in

the causation of edema in some patients with heart failure The following case illustrates this point

Case L M —The patient a sixty year-old white married Irish housewife gave a history of known hypertension for ten years and of having been treated during the preceding two years by a low protein salt poor diet She had had occasional headaches and slight dyspnea on exertion until fifteen months before her first admission when her dyspnea became markedly worse and she developed orthopnea and edema of the lower extremities In addition she suffered from anorexia and gastric distress so that she further limited her diet Her symptoms increased and she entered the hospital in May 1931 At this time she was found to be poorly nourished to have an enlarged heart with auricular fibrillation moderate peripheral arteriosclerosis marked pulmonary congestion ascites and general anasarca A diagnosis of arteriosclerotic and hypertensive heart disease with congestive failure and auricular fibrillation was made She was treated by absolute bed rest digitalization and diuretic drugs The latter were given chiefly in the form of salyrgan intravenously The 60 Gm protein low salt diet was continued but she ate very little of this In spite of a decrease in her dyspnea and orthopnea her edema persisted although it became somewhat less She went home in September 1931 where she remained in bed and continued to take digitalis.

She returned to the hospital on October 13 1931 and her condition at this time was similar to that found at her initial entry She was edematous to the waist and there was edema of the back and arms. She was placed on a Karell diet (800 cc. of milk daily) and was given digitalis in amounts sufficient to produce full digitalization and received intravenous injections of salyrgan on October 15th 17th and 20th with slight temporary diuresis after each dose.

Laboratory examination of the urine revealed a specific gravity which varied between 1 004 and 1 014 in daily examinations there was no albumin and the sediment was negative. The red blood cell count was 4 500 000 per cubic millimeter the hemoglobin 87 per cent and the white blood cell count 9800 per cubic millimeter The blood nonprotein nitrogen was 30 mg per cent and the cholesterol 160 mg per cent On October 16th the total proteins of the plasma were 2 8 per cent

In view of the finding of low plasma proteins she was placed on a 120 Gm protein low salt diet on October 21st which she took with great faithfulness when the situation had been explained to her Five days later for the first time, the edema was definitely less marked (Fig 171) The plasma proteins had risen to 4 4 per cent on October 30th and to 4 6 per cent on November 9th. By November 4th the edema was strikingly less in amount and on November 17th was practically gone. She was allowed then to sit up the edema did not recur and she was discharged without any visible evidence of fluid in her tissues a week later

At home she continued to eat adequate amounts of protein but she undertook too much activity and neglected to take digitalis regularly with the result that by January 1 1932 her cardiac symptoms, including marked edema recurred. She reentered the hospital on January 3d in very much the

same state as on her previous admissions Her plasma proteins, however were 5 8 per cent and remained above 5 per cent during the next three months while she was in the hospital The usual cardiac therapy was again instituted and an 80 Gm protein diet given her In four days the edema had definitely begun to subside and her orthopnea was less, in three weeks both had entirely disappeared and remained absent throughout the remainder of her stay in the hospital

DISCUSSION

This case illustrates the factors which may combine to produce edema in patients with heart disease When first seen, this patient presented the classical picture of congestive heart failure, including massive edema which was assumed to be entirely of cardiac origin However, in spite of complete rest, adequate amounts of digitalis and of diuretic drugs, the edema persisted without much change for the first five months she was under observation Finally it was discovered that the plasma proteins were markedly diminished, and when measures were taken to increase them, the edema promptly disappeared

There are several factors which may combine to produce the low level of plasma proteins in cases of this type The chief cause is probably malnutrition For several years this patient had had a diet with a protein content which was barely sufficient for her needs With the onset of cardiac symptoms she lost her appetite, developed indigestion, and her protein intake became further reduced On physical examination her marked degree of malnutrition was obvious

In addition to an insufficient intake of protein, the plasma proteins may be further depleted by an excessive loss Although normally the tissue fluids are relatively free of protein, it is known that under conditions of anoxemia and increased capillary pressure very significant amounts of protein may pass through the capillary walls [3, 4] The protein in transudates into the pleural and pericardial cavities may reach from 1 to 2 per cent If this fluid is removed in large quantities by paracentesis, the protein is lost with it Finally, large amounts of albumin are not infrequently present in the urine of patients with heart failure, and since this albumin is derived from the blood plasma, this is one more drain on the plasma proteins

In the case under discussion the low level of the plasma proteins were due to an inadequate intake of protein rather than the loss of protein in the urine and by removal in transudates Within a few days after a suitable protein diet was instituted the edema began to subside and the plasma proteins to rise and in four weeks the edema had disappeared (Fig 171) Although it recurred later, it was then apparently entirely of mechanical origin due to the heart failure for the level of the plasma proteins had been maintained by proper diet well above the critical level The edema on this occasion subsided promptly when proper cardiac therapy was carried out

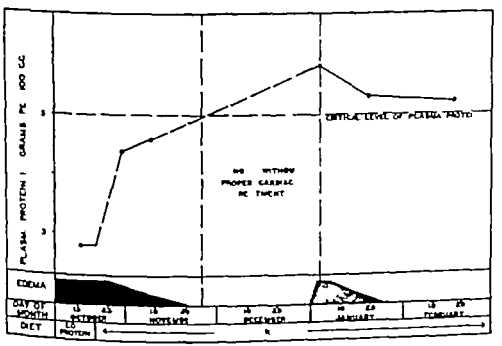

Fig 171.—The effect of a diet rich in protein on the plasma proteins and on the degree of edema in Patient L. M

Plasma protein depletion in cardiac failure has been noted before by clinical investigators and its causation and therapy discussed [2] That this condition is not uncommon will be seen from a study of Fig 172 in which are presented the results of 100 plasma protein determinations on 67 patients carried out at this Hospital in the months of December, 1931, to March 1932 Sixty two of these determinations were on patients with varying degrees of cardiac failure, of the remainder 13 were on cases of glomerular nephritis and 25 in miscellaneous cases without edema, many of which had varying degrees of

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This case illustrates the factors which may combine to produce edema in patients with heart disease When first seen, this patient presented the classical picture of congestive heart failure, including massive edema which was assumed to be entirely of cardiac origin However, in spite of complete rest, adequate amounts of digitalis and of diuretic drugs, the edema persisted without much change for the first five months she was under observation Finally it was discovered that the plasma proteins were markedly diminished, and when measures were taken to increase them, the edema promptly disappeared

There are several factors which may combine to produce the low level of plasma proteins in cases of this type The chief cause is probably malnutrition For several years this patient had had a diet with a protein content which was barely sufficient for her needs With the onset of cardiac symptoms she lost her appetite, developed indigestion, and her protein intake became further reduced On physical examination her marked degree of malnutrition was obvious

In addition to an insufficient intake of protein, the plasma proteins may be further depleted by an excessive loss Although normally the tissue fluids are relatively free of protein, it is known that under conditions of anoxemia and increased capillary pressure very significant amounts of protein may pass through the capillary walls [3, 4] The protein in transudates into the pleural and pericardial cavities may reach from 1 to 2 per cent If this fluid is removed in large quantities by paracentesis, the protein is lost with it Finally, large amounts of albumin are not infrequently present in the urine of patients with heart failure, and since this albumin is derived from the blood plasma, this is one more drain on the plasma proteins

In the case under discussion the low level of the plasma proteins were due to an inadequate intake of protein rather than the loss of protein in the urine and by removal in transudates. Within a few days after a suitable protein diet was instituted the edema began to subside and the plasma protein to rise and in four weeks the edema had disappeared (Fig. 171). Although it recurred later, it was then apparently entirely of mechanical origin due to the heart failure for the level of the plasma proteins had been maintained by proper diet well above the critical level. The edema on this occasion subsided promptly when proper cardiac therapy was carried out.

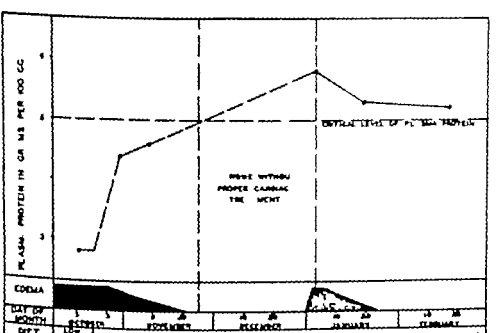

Fig. 171.—The effect of a diet rich in protein on the plasma proteins and on the degree of edema in Patient L. M.

Plasma protein depletion in cardiac failure has been noted before by clinical investigators and its causation and therapy discussed.[2] That this condition is not uncommon will be seen from a study of Fig. 172 in which are presented the results of 100 plasma protein determinations on 67 patients carried out at this Hospital in the months of December, 1931, to March 1932. Sixty two of these determinations were on patients with varying degrees of cardiac failure, of the remainder 13 were on cases of glomerular nephritis and 25 in miscellaneous cases without edema, many of which had varying degrees of

malnutrition, infection, and intoxication It will be seen in the cardiac group that although edema frequently existed when the plasma proteins were above 5 per cent because of the mechanical effect of the congestive failure, edema was always present when the proteins were below 5 per cent In some of these cases with distinctly low levels of the plasma proteins, adequate

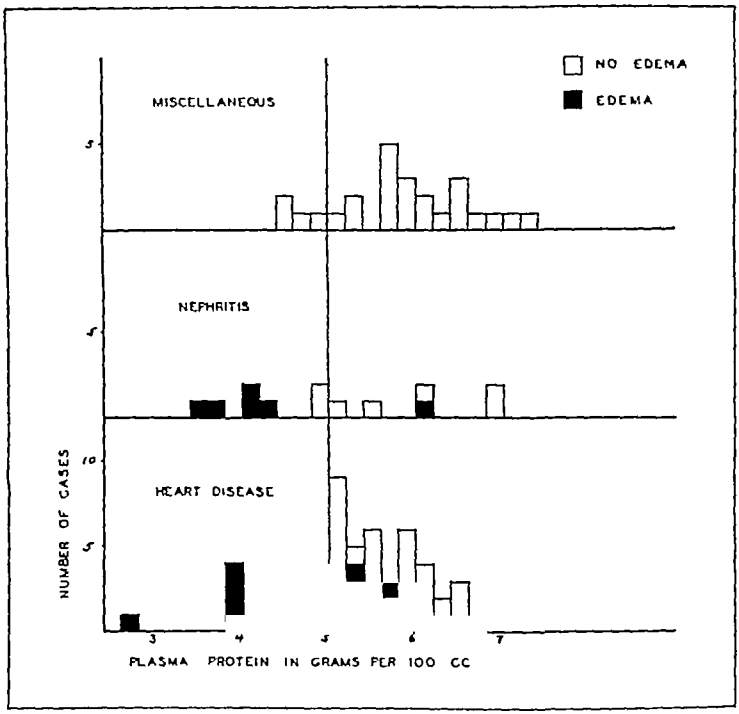

Fig 172 —One hundred determinations of the plamsa protein level in 62 patients Sixty-two of these determinations are on patients with heart disease, 13 on patients with glomerular nephritis, and 25 on patients suffering from miscellaneous conditions

amounts of protein in the diet were of assistance to supplement the usual cardiac therapy in eliminating the edema and restoring the patient to a condition of comfort and relative health

There is no definite evidence that an ample protein intake will increase renal damage in spite of the fact that some members of the medical profession still cling to the idea that it is harmful Some aspects of this problem are discussed by Minot

under the presentation of his first case in this number of the Clinics[6] Indeed, recent work has failed to indicate that a reasonable amount of protein in the diet increases renal damage in active glomerular nephritis[5] and there is much less evidence that it is deleterious in chronic cardiovascular disease Only when nitrogen retention actually exists and uremia is imminent need the protein be restricted In the routine treatment of patients with cardiac edema excessive amounts of protein are probably unnecessary If a diet containing 70 to 80 Gm of protein daily is entirely assimilated, the protein nutrition should be maintained

CONCLUSIONS

The frequency with which a low level of proteins of the blood plasma is present in patients with cardiac failure has been emphasized This condition acts to maintain and aggravate the edema which is chiefly caused by mechanical back pressure resulting from a failing heart In patients with cardiac failure in whom obstinate edema is present, attention should always be directed toward administering an adequate amount of protein in the diet in order to sustain nutrition and to keep the plasma proteins within normal limits

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CONTRIBUTION BY DRS JAMES A HALSTED AND WALTER BAUER

FROM THE MEDICAL CLINIC OF THE MASSACHUSETTS GENERAL HOSPITAL

JAUNDICE IN CORONARY OCCLUSION

JAUNDICE is a frequent accompaniment of myocardial insufficiency with congestive failure Ernstene[1] has recently given an excellent presentation concerning the probable mechanism of bilirubinemia in the various forms of heart disease, and says that in practically all cases of congestive myocardial failure there is an increase of bilirubin in the blood, although it may not be sufficient to produce obvious jaundice He does not, however, mention the occurrence of jaundice in coronary occlusion, and Robey[2] states, "It is not seen in coronary sclerosis except in those unusual combinations of anginal and congestive heart failure"

We have recently had under our care a patient with severe coronary thrombosis in whom marked jaundice appeared four days after the onset, disappearing nine days later Marked jaundice is not a common finding in coronary occlusion Because of the rarity of this combination and the interesting problem presented in attempting to explain the mechanism of the jaundice in such instances, we are reporting the case

Dr C. P H. an unmarried American physician of fifty entered the West Medical service of the Massachusetts General Hospital April 4 1932 with the complaint of substernal pain He had always considered himself a very healthy man and had had no symptoms referable to his heart or gastrointestinal tract until December 1931 when he began having slight epigastric distress associated with eructations of large amounts of gas and a feeling of distension These symptoms appeared two or three times a week directly after the noon meal and were relieved after fifteen minutes by taking soda

or by a bowel movement They were usually associated with hurried eating The patient had thought they were due to colitis

April 2, 1932, at 2 A M he was seized with a sharp pain under the sternum and precordium which disappeared in twenty minutes At 4 30 A M he was awakened by a similar pain which lasted thirty minutes At 3 30 P M on April 3d, the same type of pain returned, again unassociated with exertion He consulted a physician who suggested that he had angina pectoris An ampoule of amyl nitrite increased the pain and it began to radiate into both arms Dr Arlie V Bock, who was called to see him, found that his blood pressure was 125/80 and his pulse rate 72 There was no friction rub and the heart sounds were of good quality He gave the patient ½ grain of morphine and in the next four hours 1 grain more was taken Although the pain was relieved, the patient failed to sleep that night because of extreme apprehension He entered the hospital the next day The pain had disappeared, leaving only a feeling of soreness

His past history contained nothing of importance except that for a year or two previous he had suffered financial losses and for several weeks had worried considerably over business affairs

The physical examination showed a thick-set, somewhat plethoric, middle-aged man in no distress His color was fairly good but ashen No jaundice was detectable The pupils were small (morphine effect) and reacted to light The fundi, examined later, showed moderate sclerosis of the vessels with nicking of the veins and narrowing of the arteries The teeth were in fairly good condition and the throat was a little reddened The heart was somewhat enlarged, the left border of dulness being 2 cm outside the mid-clavicular line The rhythm was regular at a rate of 72 but the sounds were of only fair quality, and a soft systolic murmur was heard at the apex. The blood pressure was 120/80 The lungs were clear On abdominal examination, we were able to palpate the liver edge about 2 cm below the costal margin, but it was not tender Otherwise the abdomen was negative. The reflexes were normal Rectal examination was negative There was no peripheral edema The temperature on admission was 98 F , but at 7 P M it had risen to 101 F

Nothing abnormal was found on examining the urine The white blood count was 9000 with a normal differential count The red blood count was 4,750,000 and the hemoglobin was 85 per cent (Tallqvist) The Hinton test was negative.

We could not make an absolute diagnosis at the time of entrance because of the lack of positive findings on physical examination It was thought probable that the attack of pain had been much intensified by the fear of coronary disease which had been suggested to him by his first physician, the patient admitting that he did not "dare go to sleep" Gallbladder disease was considered, although with the rise of temperature to 101 F in the evening, we became increasingly suspicious of coronary thrombosis Unfortunately we could not conveniently take an electrocardiogram because the ward was not wired for it

Course—The patient was perfectly comfortable the first twenty-four hours and slept well His temperature, however, remained elevated and his

pulse rose to 100 (Fig 173) The next night (April 5 1932) at 11 30 P M, he was awakened by a severe pain in the epigastrium Nitroglycerin failed to relieve it but ½ grain of morphine relieved it after an hour His blood pressure at the time of the attack was 110/85 The next morning it had fallen to 70/40 At this time his heart was regular but the sounds were of

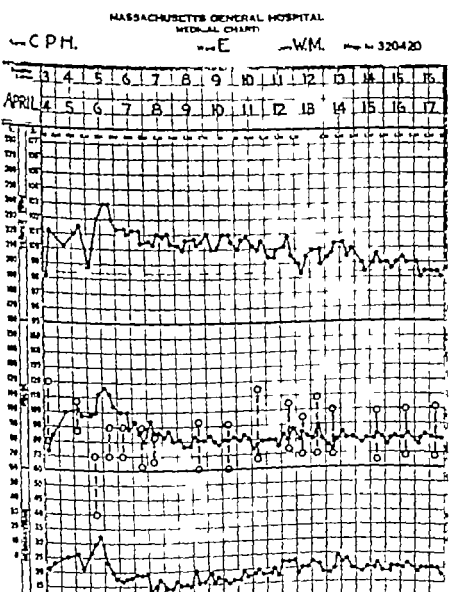

Fig. 173.—Chart showing the temperature pulse, respiration and blood pressure readings during the patient's first fourteen days in the hospital The circles connected by broken lines represent the blood pressure readings, the upper circle the systolic pressure, the lower one the diastolic pressure.

very poor quality A loud friction rub was heard over the entire precordium His pulse rate was 120 his temperature had risen to 103 F (rectal) and the white blood count to 26 000 In the afternoon his blood pressure rose to 90/70 and it remained around 100/70 during the remainder of his life. We noticed later in the day that he had become jaundiced and by the van den Bergh test there were 6 mg of bilirubin per 100 cc. (direct reaction) At this

time his liver seemed to be a little larger than on admission but it remained nontender There were a few râles at the bases of the lungs but these soon cleared An electrocardiogram taken, with a portable apparatus on April 8th, showed the characteristic early changes of coronary thrombosis with a high take-off of the T wave in leads II and III (Fig 174)

The patient's jaundice increased rapidly to a deep yellow and the van den Bergh test on April 9th was 12 mg per 100 cc. (direct reaction) At this time bile appeared in the urine After this the jaundice quickly subsided and had disappeared on April 15th, nine days after it was first noticed The

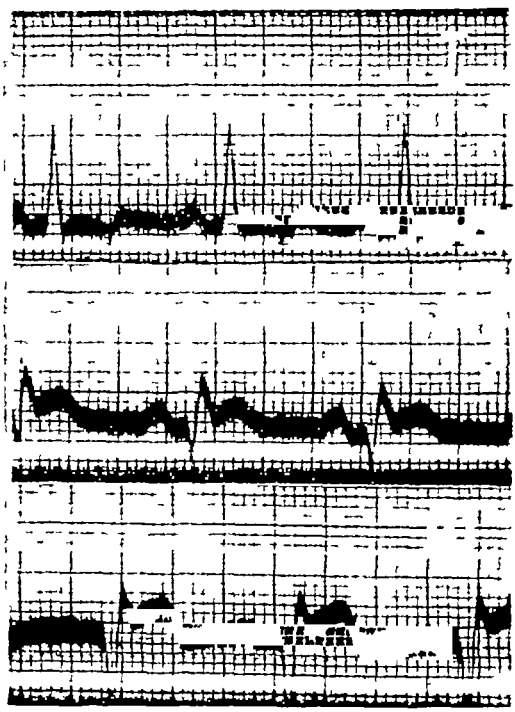

Fig 174.—Electrocardiogram taken four days after entrance into the hospital (eighth day of the disease) showing the characteristic early changes in the T wave in leads II and III

patient required morphine for a week. He was digitalized when the diagnosis of coronary thrombosis was established, and was kept on a daily dose of 1½ grains He had two more slight attacks of pain in the epigastrium which did not last more than twenty or thirty minutes and for which he did not require morphine His pulse dropped rapidly to 80 on April 9th and his temperature and white blood count slowly fell, reaching normal on April 15th

From April 16th on he felt perfectly well except for occasional slight abdominal distress relieved by enemata. His pulse rate, however, gradually rose to a level of 100 in spite of full digitalization, and he had a constant

afternoon temperature of 99 4 F (mouth) His heart sounds remained poor in quality On May 12th digitalis was omitted as he was beginning to see yellow flashes of light After the omission of digitalis he felt much better He was allowed to sit up in a chair for a half hour a day on May 16th five and one-half weeks after the onset of his illness. On May 27th he began to take a few steps. The following evening while in bed he complained of a little epigastric distress then apparently had severe precordial pain gave a few gasps and was dead

Autopsy—The important findings were in the heart and pericardium There was slight pulmonary congestion The liver weighed 2000 Cm was

Fig 175—Photograph of heart showing the dilated left ventricle, a large infarct of the posterior wall and a large thrombosis at the apex

smooth and of normal consistency There was central congestion which in places extended almost to the periphery of the lobule and slight focal necrosis evidenced by pyknosis of nuclei acidophilia and slight vacuolization of the cytoplasm of the liver cells. The pathologist, Dr Tracy B Mallory thought that except for the passive congestion all these findings could be considered agonal or postmortem changes The gallbladder and bile passages were normal and no stones were present

The pericardial cavity was completely obliterated by easily broken fibrous adhesions. The heart weighed 550 Gm The right ventricle was half again as large as normal and the left ventricle was dilated to about three

times normal size The entire posterior portion of the left ventricle, about half the interventricular septum, and the entire apex were involved in a large infarct with several shaggy mural thrombi and a large thrombus at the apex A portion just beneath the attachment of the mitral valve at the junction of the anterior and lateral surfaces was softened without hemorrhagic injection Overlying was the end branch of the left coronary artery with a small recent thrombus occluding it The myocardium of the right ventricle was flabby with a slight fibrous thickening of the endocardial portion of the interventricular septum The valves were essentially negative There was a marked

Fig 176 —Photograph of heart showing atheromatous changes and narrowing of the coronary artery At one point there was almost complete occlusion of the lumen Note the area of pericarditis overlying the entire posterior wall of the heart

degree of atheromatous degeneration of both coronary arteries with calcification, intimal ulceration, and in many places almost complete occlusion of the lumina Near the terminal portion of the left circumflex artery a small, fresh, red thrombus was found at a point where the lumen was almost pin point in size

Comment —Although the patient had had two mild attacks of pain and a very severe one before he entered the hospital, all of them coming without exertion, the diagnosis of coronary throm-

bosis could not be made until he had a fourth attack which was only moderately severe After this he presented all of the classical signs of coronary thrombosis—an extreme fall in blood pressure, feeble heart sounds, and a loud pericardial friction rub, as well as fever, leukocytosis, and the characteristic electrocardiographic changes The appearance of deep jaundice, however, was the most striking finding If it had come before his fourth attack of pain with the resultant signs of coronary thrombosis we might have made the diagnosis of cholelithiasis, and he might have been operated upon Indeed, Dr Paul D White, who saw the patient on April 7th, when all the signs of coronary thrombosis were present, believed that the jaundice might be caused by a coincident obstruction from a stone plugging the common duct. Several physicians who were friends of the patient, observing his temperature chart and the marked jaundice, believed an incorrect diagnosis had been made

The jaundice of heart disease is nearly always associated with long-standing congestive failure If it appears suddenly, or if a sudden increase in a previously existing jaundice occurs, it is usually preceded by a pulmonary infarct (Keefer and Resnik[9]) There was no suggestion of this in our patient and the autopsy showed no signs of its ever having occurred

Although we have not examined the literature in detail, we have found, in a brief survey, 11 cases in which jaundice was mentioned as a concomitant feature, without long-standing congestive failure In an excellent discussion of angina pectoris in the Lumleian lectures (1910), Osler[3] mentions 3 cases in which there was jaundice Hamburger[4] reported a case in these Clinics in 1920 in which faint jaundice appeared two days after an attack, death occurring suddenly two weeks later Neusser,[11] in his monograph on angina pectoris referred to a patient who had an enlarged liver with a subicteric color Wearn,[5] in a detailed analysis of 19 cases, observed jaundice in 2 patients Faulkner and White[6] examined the records of 30 consecutive cases of coronary occlusion and of cholelithiasis and found that there was jaundice in three of the former group Levine[7] in his published reports of 145 cases of coronary thrombosis

observed only one case in which there was any suggestion of jaundice and in this one he noted "slight icterus of the sclerae"

In only one of these 11 cases (Hamburger's) was jaundice discussed as a prominent feature and in this it was "faint but distinct" In the other 10 cases it is scarcely mentioned Thus it would seem that jaundice is a recognized feature of coronary occlusion, but is not a frequent occurrence and is usually faint when it does appear

The mechanism of the production of jaundice in heart disease has long been poorly understood The theory of obstruction of bile outflow because of extreme chronic passive congestion is not tenable when one finds that the clinical characteristics of the jaundice are usually not those of a so-called "obstructive jaundice" Furthermore, one cannot demonstrate obstruction anatomically

Rich[8] has recently offered a new classification of jaundice, dividing it into two types The first, *retention jaundice*, is the result of two factors (1) A diminished excretory power of the liver, (2) an overproduction of bilirubin Clinically it is characterized by an indirect van den Bergh reaction, an increase in the urobilin found in stools and urine, and an absence of bilirubin in the urine The second type, *regurgitation jaundice*, is caused by a reflux of whole bile from injured bile canaliculi into the blood stream This occurs when there is obstruction to the ducts or widespread necrosis of liver cells It is characterized by a direct van den Bergh reaction, a subnormal amount of urobilin in the urine and stools, and by the presence of bilirubin in the urine

Resnik and Keefer[10] have attempted to explain the mechanism of jaundice following pulmonary infarction in patients with cardiac decompensation on the basis of a sudden increase in the already existing anoxemia which has previously caused liver damage This additional damage to the liver cells is enough to produce hepatic insufficiency with inability to excrete an adequate amount of bilirubin to prevent jaundice Experimentally they produced liver damage in dogs with carbon tetrachloride, and the following day produced anoxemia by subjecting

them to low oxygen mixtures Such procedures were invariably followed by increased bilirubinemia In two of their dogs anoxemia alone without previous liver damage was shown to cause central necrosis of the liver, but it was not great enough to be followed by bilirubinemia

It has been shown in the experiments of Rich and others that anoxemia alone will produce cloudy swelling and atrophy of the liver cells Occasionally actual necrosis may result As was pointed out, Resnik and Keefer noted this in two of their dogs. In myocardial insufficiency with chronic passive congestion, anoxemia is a prominent feature and liver damage occurs It has also been shown (Eppinger) that increased blood destruction occurs in myocardial failure Thus the two factors necessary for the production of retention jaundice are present in congestive cardiac failure This is the usual type of jaundice found However, one sees occasionally in severe cardiac decompensation the characteristics of regurgitation jaundice, caused by actual liver necrosis

In the case we have discussed, the jaundice was clinically of the regurgitation type, with bilirubin in the urine and a direct van den Bergh reaction with as much as 12 mg of bilirubin per 100 cc. at one time Clinically it was apparent that he had had a large cardiac infarct, a fact substantiated by autopsy The circulation at the time his jaundice appeared was very poor, even though he did not develop congestive failure The resultant anoxemia probably was profound enough to produce actual necrosis of the liver cells with regurgitation of whole bile into the blood stream The fact that at autopsy his liver showed very little to indicate that necrosis had been present is not significant because death occurred five weeks after the jaundice disappeared, an ample time for the liver to regenerate

To us, anoxemia causing liver damage seems the most logical explanation in attempting to account for the jaundice which may develop following coronary thrombosis Assuming this theory to be the correct one, then we have another indication for the employment of oxygen therapy in the treatment of coronary occlusion

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CLINIC OF DRS SOMA WEISS AND GEORGE P ROBB

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THE TREATMENT OF CARDIAC ASTHMA (PAROXYSMAL CARDIAC DYSPNEA)[1]

The Treatment of an Attack of Cardiac Asthma in a Case of Coronary Sclerosis.—This sixty-eight year-old white male patient who now rests comfortably in bed entered the hospital in an attack of severe dyspnea. Early on the day of admittance he was awakened from his sleep with nervousness pounding of the heart sensations of substernal tightness, smothering, and pain radiating from the heart to the lower jaw After suffering for three hours in his home the patient came to the hospital in extreme apprehension and with fear of impending death He was sitting upright in bed in a frenzied struggle for air His face had an ashy cyanotic appearance and there was profuse beading perspiration over the entire body The respiration was labored with short, gasping inspiration and loud prolonged wheezing expiration and tracheal rattle He frequently coughed up frothy pink sputum The thorax was fixed in a high inspiratory position so that respiration was predominantly abdominal All the accessory respiratory muscles were contracting with great force The lower costal margins showed inspiratory retraction in striking contrast to the inspiratory bulging of the upper chest There were rhonchi crepitant and moist râles and wheezing throughout the entire chest.

The size of the heart could not be determined The pulmonary second sound was markedly accentuated and was louder than the aortic second sound. The heart rate was 120 to 130 per minute. The arterial blood pressure varied between 160 and 170 mm Hg systolic and 100 and 110 mm Hg diastolic. Otherwise the physical examination was essentially negative.

In this desperate state of affairs three hours after the onset of the attack and thirty minutes after the patient entered the hospital blood pressure cuffs were applied to all extremities close to the trunk and peripheral venous stasis was induced by raising the pressure in the cuffs to 100 mm Hg *One minute after the application of the pressure cuffs the respiration became freer and easier and the patient was less excited and restless Two minutes after application of the venous stasis further subjective improvement occurred.* The costal margins ceased to move inward. The pulmonary râles became less in

[1] Based on a study of over 80 cases of cardiac asthma.

number and the wheezing was less pronounced The heart slowed down to 96 beats per minute and the arterial pressure dropped to 120 mm systolic and 85 mm diastolic The cyanosis disappeared, and the veins of the neck were no longer engorged Five minutes after the application there was normal expansion of the chest with an almost complete disappearance of the râles The patient was comfortable, he now fell into a deep sleep

After intermittent application for thirty minutes, the pressure cuffs were removed, whereupon slight dyspnea reappeared at once, and expiration again became prolonged The cuffs were therefore reapplied, and prompt improvement resulted They were again removed after twenty minutes and the patient now remained comfortable The arterial pressure was 105/75, the heart rate 70 per minute The aortic second sound became louder than the pulmonary second sound, which was now of normal intensity

The following part of the history bearing on the attack is of interest Two years ago the patient noticed that after climbing the four flights of stairs to his room he was more dyspneic than usual, and that he also suffered from insomnia and occasional attacks of nocturnal palpitation These symptoms became gradually worse Later he noticed precordial pain radiating to his gums after exertion During the past six months he has suffered from eight or ten attacks of nocturnal dyspnea similar to but less severe than the attack described These attacks were promptly relieved by getting out of bed and "washing out his mouth" No history of lues or of rheumatic fever was obtained

Following the relief of the attack with the tourniquets, the patient felt comfortable except for moderate orthopnea He then received a full therapeutic dose of digitalis in addition to a Karell diet and theocin Following digitalization and rest, he continued to improve and experienced no subsequent attacks of cardiac asthma while under observation

Roentgen plate and fluoroscopical examination of the chest revealed enlargement of the heart, chiefly of the left ventricle, and generalized engorgement of the lung fields The electrocardiographic studies showed a left ventricular preponderance and T-wave changes suggesting coronary disease

Comment.—The severe attack of dyspnea in this case was associated with clinical manifestations of bronchial constriction and pulmonary edema Although the terms "cardiac asthma" and "paroxysmal cardiac dyspnea" are often used interchangeably, in stricter sense "cardiac asthma" should be applied only to those cases of paroxysmal cardiac dyspnea which exhibit true asthmatic type of respiration

This patient did not exhibit evidence of failure of peripheral circulation between attacks During the attack the pulmonary circulation and ventilation of the lungs became severely disturbed The application of pressure cuffs over the extremities brought

quick relief, and simultaneously the normal circulatory and pulmonary conditions became reestablished The improvement was indicated by the patient s appearance, by changes in physical signs, and in the results of measurements of a number of aspects of the pulmonary and peripheral circulation The mechanism by which the application of pressure cuffs brought relief will be discussed later

GENERAL CONSIDERATIONS BEARING ON TREATMENT

In the treatment and prevention of cardiac asthma, a knowledge of certain aspects of the pathology and physiology of the condition is essential, and these aspects are summarized below

1 An attack of cardiac asthma is precipitated by an acute, temporary imbalance between the function of the right and left ventricles This loss of normal balance of function develops through a sudden relative failure of the left ventricle, whereas the right ventricle anatomically and functionally is either normal or comparatively normal Anoxemia and insufficiency of the muscle of the left ventricle develops as a result either of decreased coronary circulation or of increased work demanded from the left ventricle by the suddenly increased peripheral vascular resistance or by an increased return of blood to the left side of the heart In numerous instances among the cases studied rise in the arterial pressure and increased respiration, with secondary increased return of blood to the right auricle, occurred simultaneously in the beginning of the attack Coronary disease, and hypertrophy of the left ventricle, alone or in combination, are always present in patients suffering from this condition Arterial hypertension and aortic insufficiency with left ventricular hypertrophy, arteriosclerosis of the left coronary artery, narrowing of the orifice of the left coronary artery due to luetic aortitis, acute thrombosis of the left coronary artery, and spasm of the coronary arteries are the most frequent pathologic findings in cardiac asthma Fusiform or aneurysmal dilatation of the aorta without narrowing of the coronary orifice, but resulting in pressure on the trachea or the large

bronchi, may also precipitate attacks of asthma—but the mechanism and clinical course of these attacks is somewhat different

2 Not all patients with the aforementioned cardiac pathology necessarily develop cardiac asthma Patients who in addition to this pathology exhibit chronic pulmonary disease, such as chronic bronchitis, emphysema, bronchiectasis, tuberculosis, or pulmonary malignancy, are particularly apt to suffer from cardiac asthma in which spasm of the bronchial tree predominates, as in bronchial asthma

3 Contrary to the general belief, cardiac asthma in its milder form is not infrequently observed Nocturnal periodic nervousness, cough, or paroxysmal pounding of the heart may be clinical manifestations equivalent to mild cardiac asthma These rather mild disturbances often are forerunners of severe cardiac asthma

4 While attacks of cardiac asthma, especially in ambulatory cases, are apt to occur during the night, they not infrequently develop during the daytime, particularly in bedridden patients During sleep, in ambulatory cases, there is a shift of the edema fluid from the lower extremities to the lungs because of change in posture

5 As with angina pectoris, excitement, physical exertion, and overeating are the most frequent precipitating factors During the night sudden awakening with excitement plays a very important rôle in setting in action the mechanism of the attack Noise, a prolonged apneic period of Cheyne-Stokes' type of breathing, a cough reflex caused by gradual accumulation of mucus in the respiratory passages during sleep, the sensation of a urinary reflex, in general, sudden changes in the respiratory and vasomotor centers and reflexes, from a state of relative depression during sleep to a state of hyperexcitability at the time of awakening, act as triggers in the attack Elevation of the arterial blood pressure, and congestion of the lungs, as indicated by râles and accentuation of the pulmonary second sound and by measurements of the pulmonary circulation, often precede the attack and are also important factors Sliding

down from a pillowed up, orthopneic position often plays a rôle We have observed several cases which developed congestion of the lung and asthma as soon as a critical level of orthopnea was reached In another group of patients, prolonged hard coughing precipitates the attack, which then proceeds independently

6 *During the attack* the arterial blood pressure, as in angina pectoris, is usually elevated, the venous pressure often is normal or may be elevated, but orthopnea is always present, the cardiac output may be normal, decreased, or moderately increased, the velocity of the blood flow through the lung is usually slowed during severe seizures, although an acceleration of blood flow may in certain cases occur These findings and accentuation of the second heart sound over the pulmonary valve suggest elevation of the pressure in the pulmonary artery From the point of view of the circulatory state, a diffuse *acute hypertensive state of the pulmonary circuit is the main characteristic of cardiac asthma*

In the precipitation of attacks several factors have to be active simultaneously The factors discussed above which act as triggers at night in starting the attack are potent only if the other predisposing factors are also present If through medication the left coronary circulation improves, and the pulmonary circulation approaches a normal state, the nocturnal precipitating factors become at once ineffective

7 *Between attacks* the peripheral circulation may be normal, but there is usually pulmonary congestion

8 Clinical and pharmacological evidence suggests that bronchial spasm is present during the attack in most cases This may, however, be absent in some instances

9 Considerable parallelism exists between the underlying pathology of cardiac asthma and angina pectoris In an appreciable percentage of cases paroxysmal dyspnea with asthma and precordial pain with radiation coexist.

10 Cardiac asthma may disappear when severe peripheral congestive failure develops as a result of secondary failure of the right ventricle

11 Evidence is available that changes in the vasomotor and pulmonary reflexes take part in the mechanism

12 In a number of instances differentiation between cardiac and bronchial asthma cannot be made As bronchial constriction often exists in cardiac asthma, the application of bronchial relaxor drugs as a differential aid is of little or no value The main difference between bronchial and cardiac asthma exists in the underlying pathology and physiology rather than in the state of the lungs during the attack

13 While recovery from the immediate attack occurs in the majority of instances, cardiac asthma may end fatally

TREATMENT OF ATTACK

The selection of therapeutic measures should be governed by a knowledge of the underlying mechanism of the attack in the individual patient The efficacy of such measures depends largely on their capacity to improve the coronary circulation and to reduce the circulating blood volume, the peripheral vascular resistance, and the bronchial spasm

Physical Measures—1 The patient should be propped up in bed, with the **body upright** or bent slightly forward In certain instances, sitting upright in a straight-backed chair, or standing with support, gives more prompt relief *Rationale* These positions improve the action of the diaphragm and lower the pressure in the pulmonary veins of the upper portion of the lungs, thus improving the pulmonary circulation and the ventilatory capacity of the lungs There is also less possibility of the edema shifting from the legs to the lungs They also diminish the return of the blood to the heart, and thus lessen the pulmonary congestion and the work of the heart Patients not infrequently discover that such positions bring relief In severe attacks they often bend the body anteriorly, thus compressing the veins of the abdomen and inducing more peripheral venous stasis

2 Peripheral venous stasis by application of **four tourniquets over the extremities** has proved to be one of the most effective therapeutic measures in our experience It rivals the usefulness

of morphine. It may promptly relieve an attack in cases in which morphine is ineffective In case of emergency towels or rubber tubings can be used The ideal technic, however, is the application of blood pressure cuffs connected in series and attached to a sphygmomanometer This technic allows the proper gauging of the pressure applied which should be just above the level of the diastolic blood pressure The pressure cuffs or tourniquets with pressure are allowed to stay on for from ten to fifteen minutes They are then released temporarily for one minute, to restore adequate circulation through the extremities Such intermittent application of ten to thirty minutes' duration is usually sufficient to prevent the return of the immediate attack The relief manifests itself not infrequently within from one to three minutes following the application *Rationale* This measure shunts a considerable portion of the blood from the congested lungs into the extremities, thus relieving pulmonary engorgement and giving the failing left ventricle an opportunity to recover It is also possible that in addition vasodepressor reflexes are set up from the extremities

3 **Pressure on the carotid sinus** may temporarily improve or occasionally relieve an attack The carotid sinus is that part of the bulbus dilation of the common and internal carotid artery, located at about the angle of the jaw, which possesses a rich and specialized afferent vasomotor innervation This measure, in our experience, has not proved very effective, but it is worth applying, especially if more adequate treatment is not readily available. *Rationale* Pressure on the carotid sinus gives rise to afferent impulses which traverse the glossopharyngeal and vagus nerves and set up a depressor reflex associated with a fall in the blood pressure and slowing of the heart. The diminished blood flow to the heart and the lowered peripheral resistance make possible the reestablishment of the balanced function of two ventricles The efficacy of this measure depends on the sensitivity of the reflex, which varies considerably in different people.

4 **Venesection** may be performed, particularly if peripheral venous engorgement exists and if there is no anemia The amount of blood removed should depend on the degree of venous

congestion, and it may be gauged by the simultaneous measurement of the venous pressure Sufficient blood should be removed to cause a distinct lessening of the venous engorgement and some relief of dyspnea In general, from 300 to 700 cc is sufficient In our experience the rapid removal of the blood by phlebotomy is more effective than by venepuncture *Rationale* Venesection reduces temporarily the circulatory blood volume and the viscosity of the blood, thus decreasing the work of the left ventricle and likewise the pulmonary engorgement The effects are less dramatic although more lasting than the relief by venous stasis

Chemical Measures—1 **Morphine** is the drug used traditionally in cardiac asthma The dosage depends on the intensity of the attack The effective dose varies between $\frac{1}{6}$ and $\frac{1}{2}$ grain (10 to 30 mg) given subcutaneously *Rationale* The mechanism of the beneficial effect of morphine in cardiac asthma is not well established It depresses the excitability of the respiratory and vasomotor centers, and thus indirectly decreases the return blood flow to the right heart It relaxes the bronchioles It is possible that it produces vasodilatation if the arterioles are in a state of constriction In our experience morphine acts primarily upon the higher centers, first allaying the excitement, then relieving the dyspnea, and finally lowering the arterial blood pressure and reducing pulmonary congestion

2 **Nitroglycerin** in amounts of 1/100 to 1/25 grain (1 to 4 mg), applied under the tongue, frequently relieves attacks, particularly when associated with extreme hypertension It is essential that it be administered in sufficient dosage to lower the arterial pressure significantly *Rationale* Nitroglycerin improves the coronary blood flow It produces arteriolar relaxation and thus lowers the arterial blood pressure, which in turn improves the functional capacity of the left ventricle

3 **Epinephrine** (adrenalin) frequently relieves attacks of cardiac asthma, particularly in the group in which bronchial spasm exists and asthmatic breathing predominates Its application, except in acute coronary thrombosis and angina pectoris, is not contraindicated The presence of arterial hypertension

does not contraindicate its judicious use, as in our experience it induces a depressor (inverted action) rather than a pressor effect in such cases A paradoxical fall in blood pressure with relief of asthma, follows its administration The effective dosage varies from 5 to 30 minims of 1 1000 solution subcutaneously As a rule, larger doses are required here than in bronchial asthma It is less effective than morphine or nitroglycerin *Rationale* In man, epinephrine in small amounts relaxes the bronchioles and arterioles Some evidence exists from animal experimentation that it relaxes the coronary arteries and that it increases particularly the coronary blood flow Its relaxor effect on the arterioles in the presence of spasm, such as exists during cardiac asthma, is particularly marked Summation of these effects beneficially influences the functional capacity of the left ventricle

4 **Intravenous digitalis therapy** in cases with desperate attacks and with severe pulmonary edema may be instituted, provided the patient has not received any of the digitalis substances before, and provided he is not suffering from acute coronary thrombosis Any digitalis body of standard potency may be given crystalline strophanthin (ouabain) in single doses of 1/200 to 1/120 grain (0 3 to 0 5 mg), or amorphous strophanthin in amounts of 1/120 to 1/100 grain (0.5 to 0 75 mg), or digitoxin in doses of 1/100 to 1/60 (0 75 to 1 mg) Other digitalis preparations suitable for intravenous administration and accepted by the Council on Chemistry and Pharmacy of the American Medical Association can also be recommended *Rationale* We have presented evidence that digitalis can reestablish the normal pressure relations in the pulmonary circuit in patients with orthopnea and pulmonary congestion even if the peripheral circulation is normal Patients with cardiac asthma exhibit such a state of the circulation

5 **Atropine** is of some value in cardiac asthma It may decrease somewhat the bronchial secretion and moisture in the lungs

PREVENTIVE TREATMENT

Between attacks therapeutic measures which prevent attacks should be introduced The aim of such therapy is to relieve

chronic pulmonary engorgement and to improve the reserve of the left ventricle

1 **Rest and digitalis therapy** should be instituted in the same manner as with other types of cardiac failure Excitement and physical exertion should be excluded, and proper restrictions in the routine activities of the patient should be introduced *Rationale* Such methods improve the cardiac reserve and decrease pulmonary congestion for obvious reasons

2 **Restriction of fluids** and administration of **diuretics** frequently result in prompt temporary or permanent disappearance of the attacks Edema, whether of the periphery or of the pulmonary tissues, should receive identical treatment Salyrgan (10 per cent) in doses of 1 cc every second day for three doses, either alone or in combination with ammonium chloride or urea in doses of 2 to 3 Gm four times daily, may be administered Theocin or other diuretics should also be tried, as one cannot foretell which of the diuretics will prove efficacious *Rationale* Restriction of fluids and use of diuretics lower the circulating blood volume and decrease pulmonary congestion just as they improve peripheral edema The lungs in patients with cardiac asthma are often water logged

3 The administration of **sedatives,** particularly in the evening, often prevents attacks Luminal in doses of 1½ grains (0 1 Gm)—or other barbituric acid derivatives—alone or in combination with ½ grain of codeine is efficacious In cases in which severe attacks recur with regularity, the administration of morphine at regular intervals under close supervision of the physician is justified *Rationale* Sedatives decrease the excitability of the central nervous system, one of the primary immediate causes of the attacks

4 **Vasodilator substances,** particularly those affecting the coronary blood flow, should be given at regular intervals Certain purine derivatives, particularly theophylline (theocin) in doses of 5 grains (0 3 Gm) three times daily for four days and to be repeated after an interval of seven days, may be recommended Sodium nitrite in doses of 1 to 3 grains (0 06 to 0 18 Gm) may be given in case there is acute elevation of the arterial pressure

Alcohol (whiskey 30 to 60 cc) if given when early prodromal symptoms appear will often abort attacks *Rationale* These substances improve the coronary blood flow and may lower the arterial blood pressure

5 Administration intravenously of 50 to 100 cc of a 50 per cent glucose solution daily or on alternate days for four or five doses repeated every two to four weeks may stop the attacks *Rationale* It is claimed that the beneficial effect of glucose depends on better nutrition of the myocardium This claim, however, is not proved Such a concentrated solution of glucose may draw fluids from the tissues and particularly from the lung, and thus cause diuresis

6 If chemical analysis of the blood indicates that the protein, and particularly the albumin fraction, is low, the patient should be placed on a high protein diet We have seen marked improvement follow such a régime *Rationale* Low protein content of the blood increases the tendency of fluid to pass into the alveolar spaces from the capillaries of the lungs Such patients are particularly apt to develop marked pulmonary edema with the attacks and to suffer from chronic pulmonary edema

7 Patients with tendency to attacks should be placed in a high orthopneic position on going to bed, and provision should be made to prevent sliding down They should not sleep in cold rooms, and in atmospheric conditions with high humidity the windows of the bedroom should be kept closed *Rationale* Cold air and humidity predispose to bronchial spasm and pulmonary congestion in these patients

8 Periodic venesection according to the technic described above plays a beneficial rôle in the prevention of attacks

Skilful therapy in cardiac asthma brings prompt relief from intense suffering, and reestablishes a series of severely deranged bodily functions In critical condition, some of the measures described may even save the patient's life at times One should remember that cardiac asthma is a syndrome depending on functional changes and that it occurs frequently during an early stage of heart failure The proper management of the patient between attacks can therefore prolong life considerably

CLINIC OF DR HENRY JACKSON, JR

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AGRANULOCYTIC ANGINA

THERE are a variety of clinical conditions which may be associated with extreme or moderate lowering of the white blood cell count In some of these, as in splenic anemia, pernicious anemia or, more rarely, Hodgkin's disease, the white blood cell count may fall to a very low level, but in and by itself it is not of vital importance, either from the diagnostic or the therapeutic standpoint. In other conditions, however, the level of the white blood cell count is of the greatest importance from both these points of view

Agranulocytic angina is one of these states In this disease, the white blood cell count drops to levels often below 1000 per cubic millimeter and the polymorphonuclear neutrophils may entirely disappear Associated with this extreme leukopenia there are usually, but not always, ulcerations of the mucous membranes of the mouth, pharynx or intestine as well as high fever, great prostration and, as a rule, in untreated cases, death in a comparatively short time In the true disease the leukopenia comes first and secondary infection follows Recurrences, if the patient survives a first attack, are common and equally liable to be fatal The etiology of the disease is unknown, and the pathology little understood

Then again, in certain patients suffering from overwhelming sepsis, such as pneumonia, especially in children, septicemia or osteomyelitis, there may ensue a marked leukopenia and in these cases the prognosis is just as unfavorable as in true idio-

pathic agranulocytic angina In this type of leukopenia the sepsis precedes and brings about the blood change The etiology and the pathogenesis of the two conditions is probably different, the prognosis essentially the same

The following case reports are presented to illustrate examples of these closely allied conditions

Case I —A widowed American woman of thirty years entered the hospital December 17, 1931 Her past history is interesting and important She was entirely well until February, 1930, when after a few days of general malaise she had quite suddenly a series of sharp chills and a temperature of 104 F The following day she had generalized muscle pains and ulcerations of the gums rapidly developed No blood studies were made at this time She was acutely ill for ten days with continuous fever and marked prostration The temperature then fell to normal and she rather gradually regained her strength and health

All went well until March 16, 1930, when she noticed that her gums were again sore. The same day she had chills, marked prostration and a temperature of 104 F Her throat was extremely painful The white blood cell count was found to be 1600 per cubic millimeter and no polymorphonuclear neutrophils were seen in the smear For four days she continued in this condition and the blood remained essentially as on entrance, but then the temperature rather suddenly dropped to normal At the same time the white blood cell count abruptly rose to 5400 per cubic millimeter and mature polymorphonuclear neutrophils to 56 per cent Convalescence was uneventful

In June, 1930, she had another attack of sore throat and extreme prostration At this time her white blood cells dropped to 650 per cubic millimeter and there was again complete absence of polymorphonuclear neutrophils During this illness superficial ulcerative lesions appeared on the hands and buttocks and she developed a left parotitis After a few days all symptoms nd signs subsided, the white blood cell count rose to a normal level and she remained well until August, 1930, when she had again ulcerative lesions in the mouth and it was found that her white blood cell count was 500 per cubic millimeter For two weeks her white blood cells never rose above 2000 per cubic millimeter and no polymorphonuclear neutrophils appeared in the blood Recovery this time was very gradual and only after several weeks was she symptomatically well She then remained in good health until December, 1931 From time to time blood counts were done in view of the past history On December 16, 1931, she felt perfectly well and was about her usual duties, but her white blood cell count was found to be 3000 per cubic millimeter with but 20 per cent polymorphonuclear neutrophils The next day she continued to feel well, but the white blood cell count had fallen still further to 500 per cubic millimeter and the polymorphonuclear neutrophils were only 2 per cent There was no obvious infection from a clinical point of view The following morning her white blood cell count was 700 per cubic millimeter, yet she still felt perfectly well She was admitted

[illegible] was given 10 cc pentnucleotide (N N R) intramuscularly every day. Following each injection she was nauseated occasionally [illegible]. The afternoon of her admission her temperature rose to 101 F and [illegible] with an intermittent temperature ranging from 101 F in the evening to 99 F in the morning (Fig. 177). On December 22d five days after entrance, she complained of considerable pain in the lower rectum and perineum. Careful examination showed no lesion. Except for this [illegible] she felt much better although the temperature remained elevated [illegible] white blood cell count had risen to 1900 per cubic millimeter and continued to rise during the succeeding days and the differential count of the

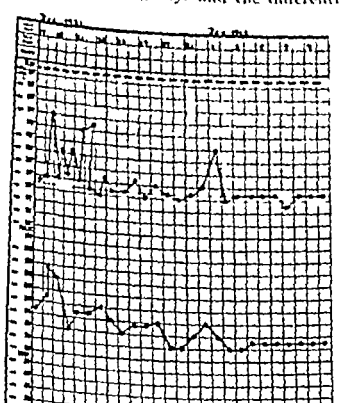

Fig. 177.—Case I. Temperature, pulse, and respiration during fourth attack.

cells became more and more normal. Preceding the rise in total white blood cell count there was a marked increase of young white blood cells, stem cells, myelocytes, and metamyelocytes. Mature polymorphonuclear neutrophils appeared only after the advent of these young cells. This early myelocyte response has been noted by Doan in his cases treated with pentnucleotide.[1] On December 26th, however, she complained of much more pain in the rectum and perineal region and a small ischiorectal abscess was found. Two days later this was opened and 2 ounces of pus evacuated. Following the operation the white blood cell count progressively fell to 3700 per cubic millim

[1] Doan, C. A. Neutropenic State. Its Significance and Therapeutic Rationale, Jour. Amer. Med. Assoc., July 16, 1932, vol. 99, pp. 194–202.

eter although the polymorphonuclear neutrophils remained 69 per cent On December 30th pentnucleotide was again started in 10 cc intramuscular doses By January 1st the white blood cell count had risen to 6400 per cubic millimeter and the patient seemed much better Uneventful convalescence ensued

The blood was very carefully followed after this attack and particularly so at the time of her menstrual periods At the time of the catamenia a sharp drop in total count occurred and there was further a decreased percentage of polymorphonuclear neutrophils At each catamenia the total white blood cell count was found to be slightly lower than at the preceding one, although between periods it rose once more to an essentially normal figure In Sep-

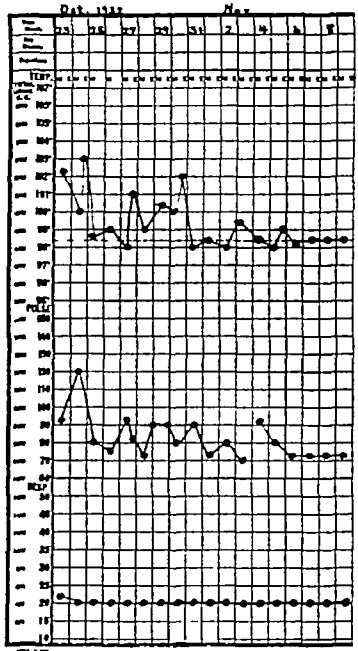

Fig 178 —Case I Temperature, pulse, and respiration during fifth attack

tember, 1932, the count fell to 3000 per cubic millimeter with but 19 per cent polymprphonuclear neutrophils At the time it was predicted that the succeeding month would usher in another attack This proved to be the case On October 21, 1932, she had a slight chill and felt poorly The next day she was better but on October 23d she had a sharp chill, severe headache, and general malaise She was immediately brought to the hospital where her white blood cell count was found to be 1200 per cubic millimeter No polymorphonuclear neutrophils were seen The temperature was 104 F (Fig 178) Aside from marked asthenia and general prostration there were no particular symptoms No ulcerations were present She was given 20 cc pentnucleotide intramuscularly and thereafter 15 cc twice a day for two days

The white blood cell count rose rather rapidly to 3000 per cubic millimeter two days after entrance and the patient seemed much better—so much so that the pentnucleotide was omitted The next day the white blood cell count was 5000 per cubic millimeter and the differential showed 38 per cent polymorphonuclear neutrophils but the following day showed no further hematological improvement The next day October 28th there was a slight fall in the white blood cell count and the day following the white blood cell count had dropped to 2400 per cubic millimeter and the mature polymorphonuclear neutrophils had entirely disappeared What explanation can we give for this sudden reversal of the picture? She had an acute upper respiratory infection with sneezing and a stuffed up feeling in the nose. It is probable that this infection drained to its site all the polymorphonuclear neutrophils of the peripheral blood and that the only partially recovered bone marrow was unable to throw out cells fast enough to overcome the demand It is interesting to note that the total number of lymphocytes and monocytes remained precisely the same—only the polymorphonuclear neutrophils disappeared Accompanying this attack there was a moderate rise of the temperature Pentnucleotide was resumed on October 28th and once more the white blood cell count started to rise and young granulocytes appeared but an access of the upper respiratory infection on October 31st again brought them to a low level without disturbing the other elements Again however young granulocytes appeared and after a slight set back on November 2d probably due to an acute bronchitis, rapidly rose until on November 8th the white blood cell count was 6000 per cubic millimeter with 69 per cent mature polymorphonuclear neutrophils. The temperature was then normal and uneventful convalescence ensued Intramuscular pentnucleotide was continued until November 5th when the great increase in young polymorphonuclear neutrophils and the marked improvement of the patient s clinical condition seemed to warrant its discontinuation Thereafter 10 Gm of nucleic acid was given daily by mouth until the white blood cell count had risen to 7000 per cubic millimeter It seems probable that the hesitant and intermittent hematological improvement was occasioned by intercurrent infections temporarily draining from the peripheral blood all the granulocytes which could be manufactured by the, but partially recovered bone marrow

Here we have a classical case of agranulocytic angina Several points are to be noticed First She had had three typical attacks prior to the present two From each she had recovered spontaneously No specific therapy had been tried during these early attacks The difficulty of attributing recovery to any given therapy is thus obvious Second The white blood cell count during the next to last attack was extremely low for two days before the onset of clinical symptoms This argues strongly in favor of a primary leukopenia with secondary infection rather than the reverse Third During her fourth attack

her white blood cell count started to rise definitely five days after the initiation of pentnucleotide therapy In the great majority of cases it is about this time that hematological improvement occurs following this form of treatment, irrespective of the previous duration of the disease In carefully studied cases, however, stem cells, myelocytes and young polymorphonuclear neutrophils appear after forty-eight hours of pentnucleotide treatment This appeared to be the case during the patient's fifth attack After the white blood cell count had risen and 69 per cent polymorphonuclear neutrophils were to be found there was a sudden drop on October 31st, when the polymorphonuclear neutrophils virtually disappeared But again, on November 2d, a sudden reversal occurred, this time apparently occasioned by a tracheitis and bronchitis Again, after complete disappearance of polymorphonuclear neutrophils there was a flood of young cells and as the temperature fell and the complications cleared, the count gradually rose In not a few cases after an initial rise of total white blood cell count there may be a sudden fall It is probable that in these instances an intercurrent infection is responsible for the drop in count Fourth There was an extraordinarily rapid development of an ischiorectal abscess during the fourth attack shortly after the white blood cell count had risen and this complication was followed by a rapid fall of white blood cells in the peripheral blood Such complications are not rare in agranulocytosis and they require the usual treatment, irrespective of the underlying conditions The development of pus at such a time is an indication of the patient's improved condition, it could not develop during the leukopenic stage It must be regarded as a sequel to recovered bone marrow activity

Case II —A married man was admitted December 22, 1931 His past and family history were unimportant Two months before entry the patient noticed that the toes of his left leg were red, swollen, and tender The condition grew worse and a month later he had a series of sharp chills Three days before admission there were again marked chills and the patient noticed that there were ulcerations and blebs on his face and buttocks On entry, aside from marked arteriosclerosis, the most important findings were superficial ulcerations on the face and both buttocks and a sharply defined gangrene

of the toes of the left foot. First the left foot was amputated and then a week later it was necessary to remove the left leg at the hip After a stormy convalescence the patient was discharged much improved on February 6 1932

After a few days at home the patient became worse. There appeared an ulceration of the left buttock which exuded thin watery serum He was readmitted to the hospital February 16 1932 At this time his white blood cells were 3000 per cubic millimeter without polymorphonuclear neutrophils The temperature was 102 F and the patient was semiconscious and very toxic.

In view of the comparatively low white blood cell count and the complete absence of polymorphonuclear neutrophils pentnucleotide was immediately started 10 cc intramuscularly twice a day for three days. At the end of this period his clinical condition appeared much better his temperature had

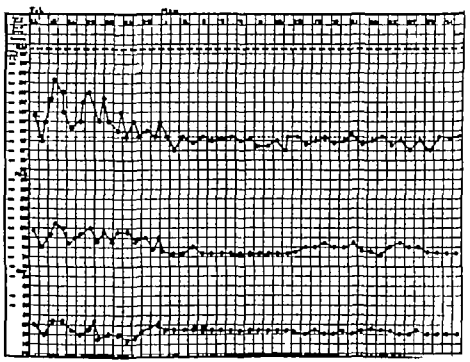

Fig 179 —Case II Temperature pulse, and respiration

fallen from 104 to 99 5 F (Fig 179) and coincidentally his total white blood cell count had also fallen to 1100 per cubic millimeter (Fig 180) The myelocytes had risen to 10 per cent indicating that the bone marrow was again actively functioning It is to be noted that the myelocytes are charted in percentage. If the total myelocytes are charted the curve is slightly modified but its significance is the same Owing to the mechanical difficulty of either intramuscular or intravenous therapeusis the pentnucleotide was reduced to 10 cc. a day The total white blood cell count rose to 5200 per cubic millimeter but fell rapidly again and the myelocytes disappeared so that on February 26th ten days after admission 40 cc. pentnucleotide was given and thereafter the same amount was administered each day for six days Following the first larger dose there was a sharp increase of myelocytes (Fig 180) and the white blood cell count rose to 9500 per cubic millimeter and it remained

essentially normal thereafter The gangrenous lesions rapidly healed, the patient recovered his strength and was discharged well on April 2, 1932

In this case there can be but little doubt but what we were dealing with an agranulocytic picture secondary to an infected gangrene in a debilitated arteriosclerotic patient There appears to be no question but that the improvement was brought about by the pentnucleotide and furthermore, in this case, there seemed to be a fairly close parallelism between the amount of

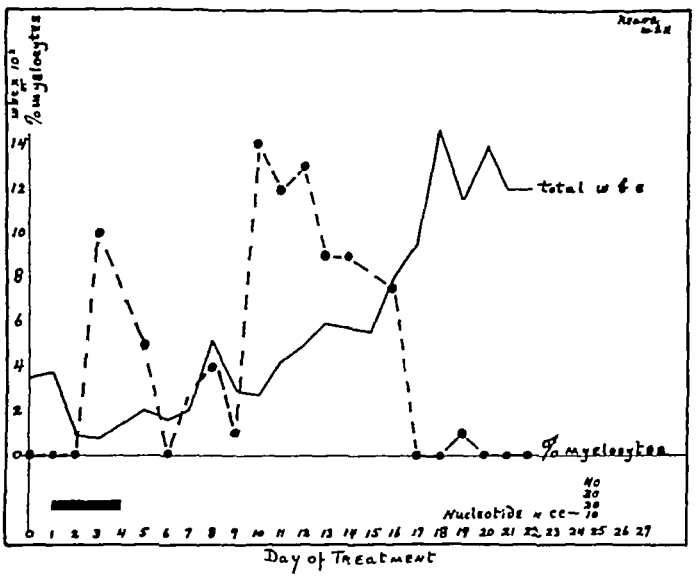

Fig 180 —Case II White blood cell counts and percentage of myelocytes in relation to pentnucleotide treatment

pentnucleotide administered and the magnitude of the myelocytic response and the subsequent increase in white blood cell count

Case III —A married Lithuanian woman of fifty-five years was admitted to the hospital on April 5, 1932 The history was obtained from relatives

The patient was apparently in good health until ten days before entry At that time she developed a head cold and a productive cough At the same time she experienced some constriction in her throat Seven days before entry she had a chill Three days later she was seen by her personal physician who found many sibilant râles in both lungs and a temperature of 101 F At the time the patient spat up bloody sputum

Physical examination on entrance to the hospital showed a well developed and nourished woman breathing heavily There were no ulcerations in the mouth. The lungs were everywhere resonant with generalized sonorous and sibilant rales There were no signs of consolidation The heart was normal Temperature 102° F pulse 120 respirations 30 (Fig 181) The white blood cell count was 1500 per cubic millimeter and the differential count showed polymorphonuclear neutrophils 0 lymphocytes 82 monocytes 13 myelocytes 5

Ten cc. pentnucleotide was administered intramuscularly the day after admission both morning and evening and thereafter 10 cc was given twice a

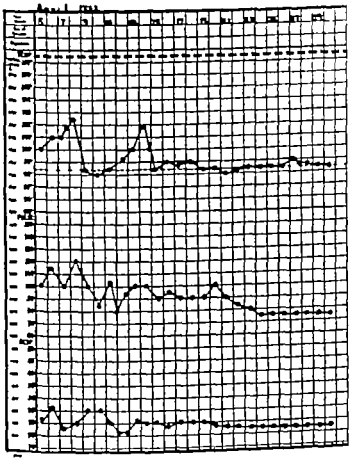

Fig 181 —Case III Temperature, pulse and respiration

day for eight days The temperature rose consistently for three days (Fig 181) after which it fell abruptly to normal to rise again temporarily eight days after admission for no apparent reason x Ray films of the lungs at no time showed evidence of consolidation and the abnormal physical signs in the chest gradually cleared

The course of the white blood cell count is seen in Fig 182

This case represents either malignant neutropenia secondary to influenza or agranulocytosis with complicating bronchitis I do not believe a positive differential diagnosis can be made

between these two conditions From a practical point of view the prognosis and the treatment is the same in either case

We have thus 3 cases—one of classical agranulocytosis, one of malignant neutropenia following sepsis and one in which the exact diagnosis is in doubt In all the prognosis was grave It matters but little whether the neutropenia be primary or secondary In all the main problem was that of raising the white blood cell count How best may this be done? To date the best method would seem to be the administration intramuscularly

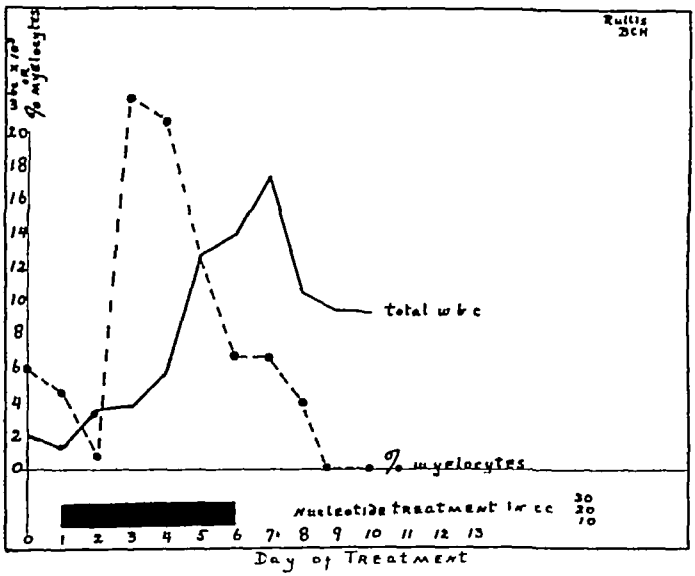

Fig 182 —Case III White blood cell count and percentage of myelocytes in relation to pentnucleotide treatment

of pentnucleotide This substance is known to stimulate white cell production in animals and a very considerable degree of success has followed its use in human cases of agranulocytosis and malignant neutropenia It will not save all cases In some there is absolutely no response But at present it appears to offer the best form or chance of recovery in these otherwise fatal conditions

These 3 cases illustrate the importance of the white blood cell count in cases of infection and in diseases of unknown nature

If the leukopenia be primary, as in agranulocytic angina, or if it be secondary to overwhelming sepsis there is grave danger ahead and it is essential that the white blood cell count be raised to normal Pentnucleotide would seem at present to be the best agent for so raising the count But one must not forget that careful nursing care and prompt and adequate treatment of complications are most important in these serious and baffling conditions

PARALYSES OF EXTERNAL OCULAR MUSCLES IN DIABETES

OCULAR palsies in diabetics, although not considered rare in the ophthalmologic clinic, are not commonly seen in the medical clinic. Paralyses of peripheral nerves, especially of the extremities, occasionally multiple,[1] are frequent, no less than 12 such cases being seen at the New England Deaconess Hospital in one year.[2] Ocular palsies are probably more common than is usually stated and the following 5 cases, observed in the months of October and November, 1932, are reported for this reason.

Case I.—Male American organist. Onset of diabetes occurred in January 1927 at the age of sixty nine years. No other cases in the family. In July 1929 blood pressure was systolic 140 diastolic 75 arteriosclerosis was consistent with his age. Wassermann was negative. he was sugar free upon a diet of carbohydrate 107 Gm. protein 57 Gm. fat 87 Gm. taking 15 units of insulin.

On March 18 1931 he waked in the morning with the left eye out of focus. Upon examination two days later the blood pressure was systolic 176 diastolic 94 and he was found to have a paresis amounting almost to paralysis of each internal rectus muscle. All other ocular muscles were normal. The left eye showed some nystagmus probably the result of reduced central vision dependent upon degeneration of the macular area of the left retina dating back some forty years. Dr. J. H. Waite considered that a very small hemorrhage centrally placed between the paired halves of the third nucleus could give just this picture.

In December 1931 paresis was still present although great improvement had occurred. On October 26 1932 the urine was still sugar free blood sugar was 0.12 per cent. weight 138 pounds and the insulin dose 24 units per day. Paresis was slight.

Case II.—Italian tailor. Onset of diabetes in January 1924 at the age of fifty three years. In June, 1932 he was first seen because of severe pain in thighs legs, worse when in bed and six months in duration. Examination

showed his blood pressure to be systolic 210, diastolic 110, heart was enlarged, both ankle jerks and knee jerks were absent, weakness of the extensors of the left toes and marked tenderness of thighs and calves were present Sensation to pin-prick was normal Wassermann negative The urine contained 2 6 per cent sugar, a very slight trace of albumin, blood sugar was 0 12 per cent and the nonprotein nitrogen was 46 mg The characteristic tremor and facial expression of paralysis agitans were present

On October 27, 1932, he reappeared with complete paralysis of the right sixth cranial nerve Other ocular nerves were apparently normal Examination of the eye showed many hemorrhages and exudate of the renal type as well as coronary cataracts

Case III —Italian housewife Onset of diabetes in July, 1924, at the age of forty-nine years No other cases in the family Hypertension was discovered in 1928, and she began insulin in January, 1928, with a dose of 35 units a day On October 24, 1932, her blood pressure was systolic 216, diastolic 144, heart was enlarged For three months she had had severe burning pain in the left leg, thigh, and back, which prevented sleep at night Wassermann was negative Knee reflexes present, but no ankle reflexes Hyperesthesia present over entire left leg

Within a few days she had developed blurred vision A complete paralysis of the right abducens or external rectus muscle was present Renal retinitis and hemorrhages were present in both eyes with marked sclerosis of the retinal vessels Phthalein test showed 30 per cent excretion in two hours ten minutes Urine contained large trace of albumin The nonprotein nitrogen of the blood was 30 mg

Case IV —German housewife, onset of diabetes in January, 1925, at the age of fifty-six years No hereditary history

In 1929 she suffered a ptosis of the right eyelid which lasted seven weeks At this time she took insulin for a year and then gave it up

On October 10, 1932, ptosis of the left eye had been present for one week Blood pressure was systolic 200, diastolic 80, heart was enlarged, arteriosclerosis was extreme as indicated by beading of the radial artery and occlusion of the left popliteal artery The urine contained 4 per cent sugar, albumin slightest possible trace, the blood sugar was 0 29 per cent, nonprotein nitrogen 37 mg , and the Wassermann was negative

A complete paralysis of the third cranial nerve was indicated by ptosis and failure of all ocular movements on the left except external rotation A high degree of myopia was present in both eyes with a corneal opacity in the left She left the hospital with a diet of carbohydrate 106 Gm , protein 45 Gm , fat 73 Gm , taking 20 units of insulin

In November, 1932, she suffered amputation of the left leg for gangrene On December 28, 1932, movements of the left eye were almost normal

Case V —Canadian factory inspector Onset of diabetes in February, 1931, at the age of sixty-four years On February 13, 1932, the urine contained 6 2 per cent sugar and the blood sugar was 0 33 per cent With 28

units of insulin a day the urine became sugar free At this time he had neuritis of the left leg with a paresis of the left iliopsoas and slight weakness of the left quadriceps On December 5 1932 the urine was sugar free but for ten days divergence of the eyes had been noted The blood pressure was 120/90 Almost complete paralysis of the left third cranial nerve was present. The pupil on this side was slightly dilated Ptosis of the left lid and inability to turn the eyeball upward or inward were present He was taking 20 units of insulin a day

In addition he had girdle pains with diminished sensation in a band about the trunk at a level with the corresponding distribution of the tenth thoracic nerve.

Examination of the retinae showed the following

1 Old perforation cornea with traumatic cataract o d.
2 Intra-ocular foreign body o d
3 Slight to moderate retinal sclerosis.

The Wassermann reaction was negative.

Summary of Case Records —Three cases were male and 2 female The youngest was fifty-eight years of age and the oldest sixty nine when paralysis occurred The duration of diabetes was 1 8 years in one, four years in 2 cases, and eight years in the other two In no case could the diabetes be called severe although in three instances insulin was required in doses varying from 15 to 35 units a day

The complications in each case were arteriosclerotic. In Case I a double paralysis of each internal rectus seemed best explained by a small area of hemorrhage, although the more common toxic effect of diabetes may have been responsible Hypertension varying from 176 to 216 in terms of the systolic pressure and from 75 to 144 for the diastolic pressure was present in each instance Retinitis of both diabetic and renal types were present in two The Wassermann reaction was negative in all.

In 3 cases the diabetes was not controlled when paralysis developed In Case I, on the contrary, diet had been faithfully followed, and he apparently suffered a true cerebral hemorrhage rather than a toxic neuritis

In Cases II and III peripheral neuritis or "neuralgia" involving the left leg were present at the same time Case IV had previously suffered a paralysis of the third nerve on the opposite side Case V had girdle pains and paresthesiae suggesting transverse myelitis

Discussion—Naunyn[3] devoted 30 pages to the effects of diabetes upon the nervous system as illustrated by neuralgias, neuritis, sciatica, paralyses of cranial nerves, polyneuritis, pseudotabes, and pseudosyringomyelia Similarly Labbe,[4] whose large experience exemplifies the clinical medicine of Paris, and Von Noorden and Isaacs,[5] from a large German clinic, ascribe considerable importance to the effect of diabetes upon the central and peripheral nervous systems

Mauriac et al[6] in a recent review of the nervous complications of diabetes points out the great variety of neurological lesions affecting almost all parts of the nervous system accompanying diabetes He notes the frequent occurrence of ocular palsies Herschmann[7] states that the relation between latent diabetes and neurological lesions of unexplained etiology is not rare He cites cases as young as twenty-eight years in which hyperglycemia without glycosuria was found in association with such conditions as peripheral neuritis and, in one instance, combined system disease without anemia The place of such "latent" diabetes in the differential diagnosis of obscure nervous lesions deserves greater emphasis than it has received in the past

Yet descriptions of paralyses of cranial nerves in diabetics are few Naunyn mentions 5 cases of paralyses of the facial nerve in his own practice Unlike paralyses of the muscles of the extremities which begin gradually with neuralgia and progress to paralyses, the facial paralysis developed suddenly in full magnitude without pain The paralyses developed uniformly when the diabetes was not under control and when the urine was not sugar-free However, the course was favorable In one case, within fourteen days of the development of paralysis, typical electrical reactions of degeneration appeared Yet recovery was nearly complete in two months He also refers to 3 cases reported by Gregoire,[8] of which one reported earlier by Paul, occurred in a patient who had suffered one year previously from an isolated paralysis of the trochlear nerve Bernhardt[9] reported 2 cases of his own and 4 cases from the literature

Recently a patient at the Deaconess Hospital, Case No 6876, illustrated the recurrence of paralysis of the facial nerve

He is an American lawyer, whose diabetes began in April, 1928, at the age of sixty five and one half years His diabetes is of the hereditary type and may have begun before its recognition in April, 1928 He had a paralysis of the left facial nerve in 1925 and again of the right facial nerve in 1928, with good recovery in both instances

Spear[10] reports a case in which a man forty-eight years of age was admitted to the hospital, conscious, but drowsy, with frequent spasms of the facial muscles and aphonia of two days' duration, there was also slight paresis of the facial muscles on one side It was found that renal function was good, but the urine contained sugar (10 per cent) and acetone bodies The fasting blood sugar was 0 21 per cent Under treatment with insulin and diet, the urine became sugar free and the fasting blood sugar fell to 0 086 per cent The speech became normal and the facial spasm ceased within two weeks The patient was discharged on a fairly high carbohydrate diet and insulin The symptoms in this case suggest a threatening uremia but the urea concentration test showed renal function to be normal, and there were no cardiovascular changes

Evidently paralyses of the facial nerve have come to the attention of students of diabetes almost as frequently as have lesions of the cranial nerves supplying the external ocular muscles

Paralyses of the external ocular muscles occur in the following order of frequency according to Von Noorden and Isaacs First, the abducens, second, the oculomotor, and, third, the trochlear Combinations of paralyses of external and internal ocular muscles are rare Von Noorden saw among 7 cases two instances of involvement of the pupillary and ciliary muscles He considers the condition due to a peripheral disturbance and notes the favorable prognosis Dieulafoy[11] cited 58 cases of ocular palsy reported by various authors and considered paralysis of the sixth nerve most typical of diabetes Cases II and III in this series were due to paralysis of the sixth nerve Cases IV and V represented a complete paralysis of the left third cranial nerve and Case I with paralysis of both internal recti probably was explained by a small hemorrhage so placed

as to involve both halves of the third nucleus The latter has not made the relatively rapid recovery in the course of six to ten weeks, which is the rule in ocular palsies due to a toxic effect upon the nerve rather than a hemorrhage Thus Case IV recovered from her first complete paralysis of the right third nerve in seven weeks

Diagnosis —The occurrence of paralysis of an ocular muscle or muscles in a diabetic indicates the need for special study The paralyses due solely to a toxic effect exerted by diabetes rarely are associated with pain and almost always develop suddenly Recovery is the rule within a short period and is influenced markedly by diabetic treatment In the first case of Schick and Silbermann,[12] although the urine was sugar-free, they noted improvement when under diabetic dietary treatment the fasting blood sugar fell from 0 22 to 0 16 per cent Severe migraine sometimes has occurred with attacks in nondiabetic cases Other causes of such paralyses must be sought as follows

1 Vascular lesions in the neighborhood of the nuclei Sosman and Vogt[13] reported 20 cases of aneurysm of the internal carotid artery or arteries composing the circle of Willis from the Peter Bent Brigham Hospital Nine of these cases had partial or complete paralyses of the third nerve among the physical findings Pain and exophthalmos were important symptoms The recognition of these aneurysms by roentgen examination depends upon (1) erosion of bone adjacent to the aneurysm and (2) calcification in the wall of the aneurysm appearing as fine, curvilinear shadows easily recognizable as being in the wall of a cystic structure They record 89 aneurysms of the internal carotid or adjacent arteries in a review of the literature Karplus[14] refers to a nondiabetic case with migraine and paralysis of the third nerve, in which at autopsy an aneurysm at the base of the brain was found Small areas of hemorrhage, ischemia or thrombosis due to arteriosclerosis may explain the condition in the cases with hypertension and vascular disease

2 Tumor Karplus refers to a number of cases of periodic paralysis of the third nerve In one of his 2 cases (nondiabetic) at autopsy a neurofibroma of the third nerve was found In the

remarkable case of Schich and Silbermann a diabetic with three separate attacks of paralysis of the third nerve x ray showed a large area of calcification in the center of the sella turcica, which was, however, of normal size In my Case IV similarly two irregular areas of calcification within the sella appeared in the roentgenogram She had had two attacks of third nerve paralysis No other indications of a tumor were observed, but her case will be followed further

3 Hypoglycemia The double vision due to hypoglycemia is temporary and quickly relieved by the administration of glucose either by mouth or by vein Zernik[13] recently reported 3 cases

4 Inflammatory lesions at the base of the brain Infection of the petrous portion of the temporal bone as in Gradenigo's syndrome or the onset of polioencephalitis (as in a nondiabetic case cited by Dieulafoy) should be considered

Conclusions.—1 Five cases of paralyses of external ocular muscles are reported, of which one was due to hemorrhage The coincidental occurrence of other "neuritic" lesions in these cases is noted

2 Etiologic factors of importance are the duration of the diabetes, age of the patients, the occurrence of hypertensive vascular disease.

3 Careful diagnostic study is needed to eliminate tumors and infectious lesions at the base of the brain

4 Treatment consisting of the use of insulin and dietary measures gives beneficial results within a few weeks in cases due solely to diabetes

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN DIPHTHERIA

IT IS the purpose of this report to show the correlation between the clinical and the electrocardiographic signs in diphtheria myocarditis The discussion will be limited to the so-called "late type of circulatory failure," the term "early circulatory failure,"[1] which has been applied to certain signs appearing during the initial febrile stage placing, in our opinion undue emphasis on an incidental feature of the toxemia

The underlying pathology of diphtheria myocarditis which has been well described by Warthin[2] provides an explanation for some of the peculiar clinical features of the disease In brief, the acute cardiac lesion consists of a primary toxic parenchymatous degeneration of the conducting and contractile tissues. No special affinity is shown pathologically for either apparatus The second state consists of a reparative inflammation called forth by the injured tissue The degenerated cells act as foreign bodies and are quickly surrounded by infiltrating phagocytes At the same time the remaining muscle fibers show evidence of active regeneration If the primary toxic injury has been extensive, the degree of reparative inflammation is correspondingly increased and may be so intense as to choke off the nutrition of the healthy muscle fibers which remain It is this pathologic paradox by which the reparative process actually aggravates the original injury which accounts for the delayed onset of clinical signs of diphtheria myocarditis The initial toxic degenerative changes in the heart do not ordinarily

produce any recognizable clinical or electrocardiographic signs The second or infiltrative phase, however, which occurs after the storm of fever and toxemia is over is characterized by a striking clinical picture

The clinical signs of diphtheria myocarditis usually appear with startling suddenness in the convalescent patient from one to three weeks after the onset of the disease Their appearance often coincides with the onset of paralysis of the palatal and other muscles The most constant features are pallor, vomiting, epigastric pain, apathy, and restlessness There is invariably a well-marked drop in both systolic and diastolic blood pressures and, on examination of the heart, a faint first sound and gallop rhythm Arrhythmias of various sorts are common

These clinical signs are, in our experience, invariably associated with changes in the electrocardiogram As might be expected from the histopathologic changes the electrocardiogram shows evidence of widespread cardiac damage involving auricle, ventricle and conducting tissues In certain cases the predominating effect is on the sino-auricular node, in others on the auriculoventricular node or the intraventricular conducting system In a single case one may observe all of these effects at the same time Indeed, in no other condition does one encounter such a wide variety of electrocardiographic changes

The most useful feature of the electrocardiogram is in prognosis for it furnishes a rough quantitative index of the degree of cardiac damage It is also of value in following the progress of individual cases One might expect that with such a delicate instrument as the string galvanometer one might be able to pick up the very earliest evidence of cardiac damage but in our experience electrocardiographic signs have not preceded clinical signs with any degree of constancy Although we have had no cases with clinical signs of diphtheria myocarditis who did not exhibit electrocardiographic signs we have had a few cases which showed minor electrocardiographic changes which never developed clinical signs In several cases in which daily records were taken the first signs appeared simultaneously in the electrocardiogram and the physical examination

The 4 cases described below illustrate the type of information which the electrocardiograph furnishes in diphtheria

Case I.—A seventeen year-old boy was admitted on May 31 1931 on the fifth day of the disease with a diagnosis of faucial diphtheria On admission the heart was not enlarged there were no murmurs and the heart sounds were of good quality at a rate of 80 beats per minute He was given 50 000 units of diphtheria antitoxin intramuscularly The body temperature reached 100 F (38 C) by axilla on the day of admission and on the succeeding day but remained normal thereafter On the second day in the hospital and sixth day of the disease the heart rate had fallen to 48 beats per minute and the blood pressure was 90 mm Hg systolic and 40 mm Hg diastolic. On the next day the blood pressure was 78 mm Hg systolic and 30 mm Hg diastolic and it remained at this level for a week after which it gradually rose

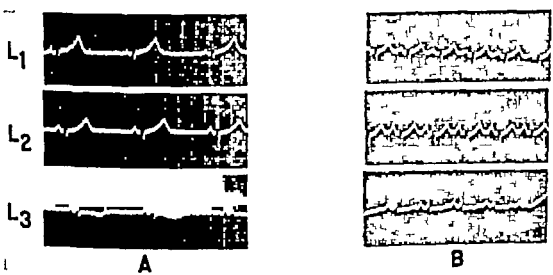

Fig 183.—Case I A Seventh day Sinus bradycardia. Rate 54 B Following injection of 1/25 grain atropine intravenously Rate 115

to 100 systolic and 40 diastolic. The heart rate remained at a level of about 50 beats per minute for the following ten days it then rose to about 60 per minute for a week and finally resumed a level between 75 and 80 beats per minute. The heart sounds were never abnormal and there were no other signs pointing to cardiac involvement Except for a transient palatal paralysis convalescence was uninterrupted and he was discharged well on the thirty-seventh day

Repeated electrocardiograms (Fig 183 A) showed only a simple sinus bradycardia with normal conduction throughout pointing to a depression of the sino-auricular pacemaker without involvement of the conducting tissues or myocardium. In this case the electrical record was quite reassuring in the face of an unusually slow heart rate which under the circumstances would naturally arouse some concern The mechanism of the cardiac slowing appeared to be a predominance of the vagal inhibitory effect on the sino-auricular node for the intravenous injection of 1/25 grain of atropine sulphate

produced a prompt and transient rise in the cardiac rate to 125 beats per minute (Fig 183, B)

Case II —A three year-old boy admitted on June 16, 1932, on the seventh day of the disease, with a diagnosis of late nasal and faucial diphtheria The axillary temperature was normal and remained so throughout his stay in the hospital The pulse rate on admission was 92 per minute The heart was not enlarged to percussion, the sounds were regular and of good quality and there were no murmurs The blood pressure was 88 mm Hg systolic and 58 mm Hg diastolic The lungs were clear and examination of the abdomen was negative He was given 30,000 units of diphtheria antitoxin intramuscularly

Two days later it was noted that the heart rate was rapid and irregular and the first heart sound was weak, approximating the second sound in quality There were no murmurs The blood pressure was 74 mm Hg systolic, 44 mm Hg diastolic An electrocardiogram taken the same day (Fig 184, A) showed a slow and irregular auricular rhythm with a rapid, independent, regular ventricular rhythm occasionally interrupted by impulses arising in the auricle In other words the picture was that of depression of the sino-auricular pacemaker without interference with conduction During the following week he was given daily intravenous injections of 40 cc of 50 per cent dextrose solution with from 5 to 10 units of insulin However, he developed increasing signs of diphtheria myocarditis as evidenced by waxy pallor, lethargy, vomiting, tenderness in the right upper quadrant and a well-marked gallop rhythm at the apex of the heart The blood pressure fell to 70 nm Hg systolic, 44 mm Hg diastolic

On the twelfth day the electrocardiogram (Fig 184, B) still showed a relatively slow and irregular auricular rhythm with a rapid and largely independent ventricular rhythm The ventricular complexes, however, showed distinct changes consisting of diminished amplitude, slurring and notching of the Q R S complexes in all leads, and a low origin of the T-wave in leads I and II These signs point to involvement of the ventricular myocardium Three days later the rate began to slow from its previous level of about 155 to about 95 beats per minute Although this drop followed the administration of digitalis (8 grains of the powdered leaf by mouth in three days) it was not thought to be due to it because the dominant rhythm remained as before in the auriculoventricular node

On the fifteenth day the amplitude of the ventricular complexes had shown a further decrease (Fig 184, C) and on the eighteenth day this was even more marked (Fig 184, D) and was associated with well-marked delay in intraventricular conduction although the sinus node had resumed its rôle of pacemaker From this time on the clinical signs of diphtheria myocarditis began to diminish The heart sounds improved in quality, the gallop rhythm disappeared, the blood pressure rose to 100 mm Hg systolic, 50 mm Hg diastolic The improvement in physical signs was associated with improvement in the electrocardiogram as evidenced by return of the intraventricular conduction time to normal and increase in the amplitude of the ventricular complexes The last electrocardiogram, taken on the twenty ninth day

showed only relatively minor T wave abnormalities and left axis deviation (Fig 184 E) A 6-foot roentgenogram taken at this time showed well marked cardiac enlargement particularly in the region of the left ventricle This patient subsequently developed extensive paralysis involving the palate

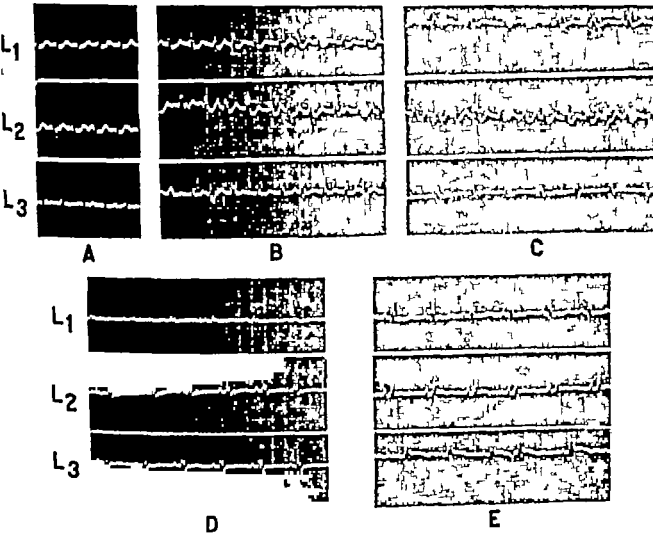

Fig 184 —Case II A Ninth day A V Nodal tachycardia Rate 168 Slow and irregular auricular rhythm B Twelfth day A V Nodal tachycardia frequently interrupted by impulses arising in the auricle Ventricular rate 160 Q-S 0 08 sec. Slurring of R wave in lead I and notching in leads II and III with diminished amplitude in all leads. Low origin of T waves in leads I and II C Fifteenth day Almost complete A V dissociation Auricular rate 103 Ventricular rate 115–160 Amplitude of Q R. S complexes further diminished D Eighteenth day Normal sinus rhythm Rate 85 P R interval 0 12 sec Very low voltage of Q R. S complexes. E Twenty ninth day Normal sinus rhythm Rate 94 P R interval 0 12 sec. Q S interval 0 08 sec. T_1 low T_3 slightly inverted with upward convexity of S-T T_3 high origin Left axis deviation (marked) Auricular premature beat lead III

eye muscles, and finally the diaphragm After several days of labored respiration he died the respirations ceasing before the heart No autopsy was obtained

This case illustrates the close correlation between the clinical and electrocardiographic evidence of cardiac involvement in diphtheria It also illustrates the common but not constant correlation between the severity of the cardiac lesion and the extent of the paralysis Furthermore, it exhibits what has been in our experience the maximum electrocardiographic evidence of heart damage with apparent cardiac recovery

Case III —A four-year-old girl was admitted June 22, 1931, on the fifth day of the disease with a diagnosis of faucial diphtheria She had received 10,000 units of diphtheria antitoxin the day before On admission the axillary

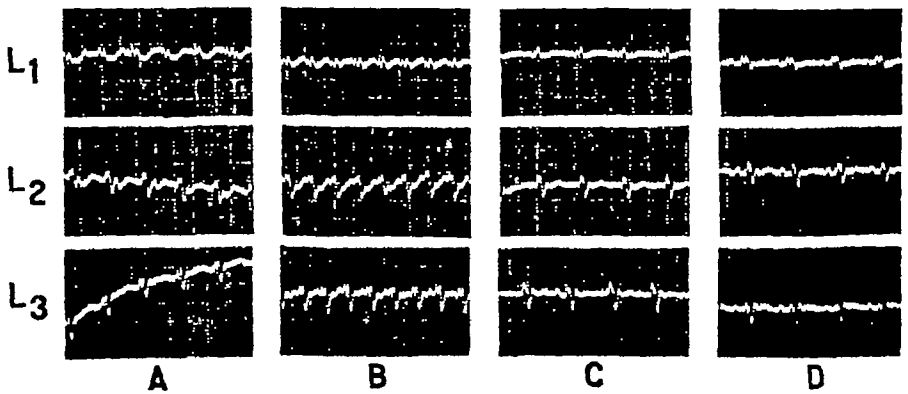

Fig 185 —Case III A, Ninth day Complete A-V dissociation Auricular rate 136 Ventricular rate 150 Q-S 0 12 sec Left bundle branch block Low voltage B, Tenth day Auricular flutter with 1 1 response Rate 240 C, Eleventh day A-V nodal tachycardia interrupted by sporadic auricular contractions Rate 134 Q-S 0 11 sec Intraventricular block. Low voltage D, Twelfth day Sinus tachycardia Rate 120 P-R interval 0 13 sec Q-S interval 0 11 sec Intraventricular block Low voltage

temperature was 100 5 F (38 5 C) and the pulse rate was 126 beats per minute The heart sounds were regular, of good quality and there were no murmurs She was given 40,000 units of diphtheria antitoxin intramuscularly The fever subsided on the second day and the pulse rate dropped to about 110 beats per minute. During the succeeding few days there was nothing to indicate trouble ahead Four days after admission, however, on the ninth day of her disease she suddenly developed marked apathy, pallor, a mild bilateral palatal paralysis and enlargement of the cardiac area of percussion dulness to the left The heart sounds were rapid and regular with a distinct gallop rhythm and there was tenderness in the right upper quadrant, although the liver was not felt The blood pressure was 48 mm Hg systolic and 35 mm Hg diastolic.

The first electrocardiogram taken on the same day, showed complete auriculoventricular dissociation low voltage and left bundle branch block (Fig 185 A) This record indicated at once that the myocardium was so severely damaged that recovery was unlikely On the following day she began to vomit and the electrocardiogram showed auricular flutter with a regular ventricular response of 240 beats per minute (Fig 185 B) The blood pressure had sunk to 40 mm Hg systolic, 18 mm Hg diastolic. Five ampules of digalen were administered subcutaneously during the next twenty four hours The following day the patient seemed better The pulse rate had dropped to 113 per minute and the blood pressure had risen to 56 mm. Hg systolic and 24 mm Hg diastolic. The electrocardiogram showed that auricular flutter had been succeeded by auricular standstill with only sporadic auricular contracting and auriculoventricular nodal rhythm (Fig 185 C) On the following day the twelfth day of the disease, sinus rhythm had returned (Fig 185 D) and the blood pressure reached 66 mm Hg systolic and 36 mm. Hg diastolic However she developed signs of consolidation in the right lung and died on the fifteenth day apparently from pneumonia. There were no signs to indicate that the pulmonary complication was embolic in origin Unfortunately no autopsy was permitted

This case illustrates the wide variety of electrocardiographic changes which may occur in the course of diphtheria It also shows that the heart is by no means the only organ which suffers from the late effects of diphtheria toxin and even after the heart has begun to improve, the patient may succumb to the direct or indirect effect of the toxin on other organs

Case IV —A twenty-six year-old machinist admitted on April 23 1931 on the fourth day of the disease, with a diagnosis of faucial diphtheria. He was given 60 000 units of diphtheria antitoxin intravenously The heart sounds were regular but the first sound was faint. The blood pressure was 114 mm Hg systolic, 34 mm Hg diastolic. The axillary temperature fluctuated between 99 and 100 F for three days and then remained at a normal level. On the tenth day of the disease he appeared very pale and it was noted that the first sound at the apex had become very faint, the blood pressure had dropped to 102 mm Hg systolic, 64 mm Hg diastolic. Synchronous with these circulatory signs there appeared a paralysis of the right side of the palate.

Daily electrocardiograms had been taken on this case since admission and the first abnormality appeared on the same day as the first clinical signs of myocardial involvement (Fig 186 A B) This consisted of a prolongation of the P R interval to 0.22 second.

During the course of the next few days the patient became listless and the blood pressure dropped to 80 mm. Hg systolic, 40 mm Hg diastolic. Parallel with the clinical signs of increasing myocardial involvement the electrocardiograms showed well marked alterations in the ventricular com

plexes consisting at first of a high take-off of the T-wave in leads II and III with a low take-off in lead I (Fig 186, C) followed by inversion of T-waves in all leads with upward convexity of the S-T interval and diminution in amplitude of the Q R S complexes (Fig 186, D) The whole sequence of changes in the ventricular complexes closely simulated those seen after an acute coronary thrombosis

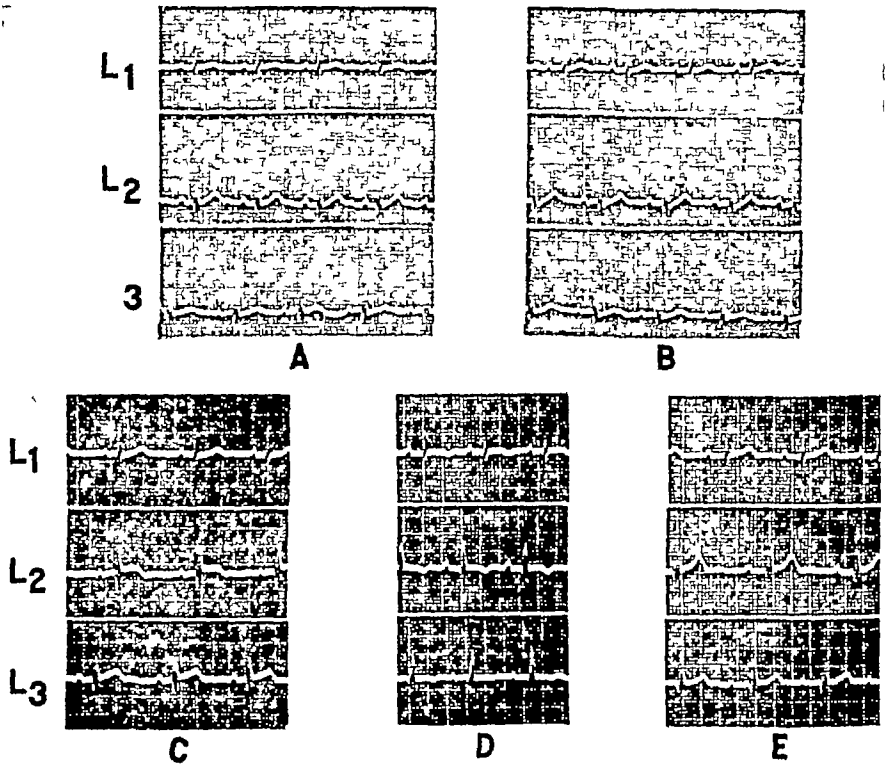

Fig 186 —Case IV A, Ninth day Normal sinus rhythm P-R interval 0 20 sec B, Tenth day P-R interval 0 22 sec C, Twelfth day Low origin of T-wave in lead I, with high origin in leads II and III D, Twenty-fourth day Marked diminution in amplitude of Q R S complexes T-waves inverted in all leads with upward convexity of the S-T interval E, Three hundred and fifty-sixth day P-R interval 0 24 sec High origin of T-wave in leads II and III

Clinically, the patient began to show improvement in the circulatory system on the twenty-second day of the disease, the first heart sound becoming louder and the blood pressure rising By the twenty-fifth day, all clinical signs of myocardial involvement had disappeared although a ciliary paralysis persisted for another month and paresthesias of hands and feet were still present on discharge from the hospital on the one hundred and first day It

is an interesting feature of this case that the rapid clinical improvement in the cardiac signs was not associated with parallel reversion to normal in the electrocardiogram The electrocardiographic evidence of myocardial changes was much slower in disappearing than the clinical signs a record taken four days before discharge on the ninety seventh day of the disease showing a high take-off of the T wave in lead II In an attempt to ascertain how long these electrocardiographic changes persist we have asked this patient to return to the clinic on several occasions for follow up The last record taken on April 30 1932 practically a year from the onset of his diphtheria showed a persistence of the high take-off of T_3 and a prolonged P R interval of 0 22 to 0 24 second (Fig 186 F) The patient at this time had returned to his work as a machinist and had no cardiac symptoms

What is the significance of the persistence of these abnormal electrocardiographic signs? Does it mean that the myocardium has been irreparably damaged? Does it support the theory that diphtheria is an important factor in heart disease of later life as suggested by some[3] This important problem cannot yet be answered with assurance but our own experience with this and 2 other cases tempts us to offer a tentative suggestion We have had 1 other case in which delayed auriculoventricular conduction persisted for at least three months following diphtheria although the patient was clinically well and back at work The other case is that of a woman of thirty years who developed permanent complete heart block with diphtheria twenty three years ago at the age of seven She has lived an active life and gone through a normal pregnancy without signs of myocardial insufficiency These cases suggest that while the cardiac muscle fibers may be able to regenerate completely perhaps the more highly specialized conducting tissues are not able to do so and the patient is left with a conduction disturbance which does not mean persistent myocardial disease

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CLINIC OF DR J LERMAN

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LYMPHOMA OF THE THYROID REPORT OF TWO CASES

Among the numerous forms of neoplastic involvement of the thyroid, lymphoma is one of the rarest The diagnosis, as a rule, cannot be made clinically from examination of the thyroid itself It is usually made from pathologic examination of the specimen removed at operation or at autopsy, or indirectly because of involvement of the lymphoid system in other parts of the body The following 2 cases are of interest both because of their rarity and because they illustrate several important points in treatment and prognosis

Case I.—Let us consider the first case Mr D a fifty three year-old married Canadian grocer first entered the hospital August 30 1928 complaining of difficulty in swallowing and in breathing Symptoms began four months previously with a dry irritating cough poor appetite, and asthenia Two months later he developed soreness over the sternum and difficulty in swallowing both symptoms becoming progressively worse. One month before entry he noticed a swelling in his neck which was large enough to interfere with the buttoning of his collar Two weeks later breathing became difficult, he began to wheeze and coughed up blood-streaked sputum There was no marked loss of weight. He had always been nervous and for a year or more had suffered from dyspnea and palpitation on exertion

Examination showed a well-developed and well nourished man in no distress. The right pupil was larger than the left but both were regular and reacted normally There was fulness in the region of the thyroid. The isthmus was hard nontender and easily mapped out Both lobes were generally enlarged and contained a few small hard nodules The gland was not adherent to adjacent structures The heart and lungs were negative except for increased supracardiac dulness The blood pressure was 125/75 There were no abnormal glandular enlargements The white blood cell count was 8850 per cubic millimeter and the basal metabolic rate minus 5 per cent. The roentgen ray showed no evidence of substernal goiter or enlargement of the thymus. The hilus shadows were slightly thickened but showed no definite lesion

A preliminary diagnosis of carcinoma of the thyroid was made and an exploration of the neck undertaken by Dr R H Miller The tumor in the thyroid proved to be hard and very extensive, growing into the prethyroid muscles, extending down behind the left clavicle further than it could be felt by the finger, and surrounding the carotid sheath posteriorly on both sides It seemed unwise to attempt removal Consequently a biopsy, only, was done

At first the pathologist thought that the character of the tissue was consistent with carcinoma But more careful study of the slides indicated the true nature of the condition Microscopically (Fig 187), the thyroid

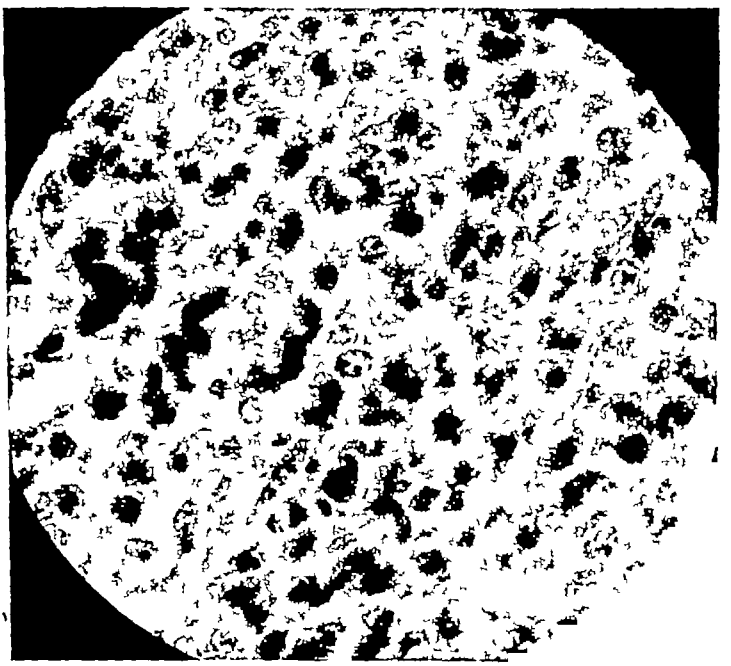

Fig 187 —Photomicrograph showing structure of thyroid in Case I

tissue was completely replaced by tumor consisting of round cells with large vesicular nuclei and scanty cytoplasm, held together by a very slight connective tissue stroma The cells were slightly larger than mature lympho cytes and were consistent in morphology with lymphoblasts Mitotic figures were infrequent An occasional lymphocyte was present Diagnosis Lymphosarcoma

The patient made an uneventful recovery and was discharged September 10, 1928 Roentgen-ray treatment was advised and he received a full erythema dose over front and back of neck and substernal region in six divided treatments from September 4th to 13th The tumor disappeared rapidly so that at the end of a month all symptoms of tracheal and esophageal pressure

had disappeared and there remained a large lima bean sized mass of thyroid tissue on the left side and a small bean sized one on the right side. At the end of nine months there was no palpable thyroid tissue

He has been followed to date at frequent intervals At present he fails to show any evidence of recurrence of the thyroid tumor or any glandular enlargements. He is in good health and has maintained his weight Roentgen ray examination of the chest and long bones fails to show any abnormality There is no evidence of myxedema and the last basal metabolic rate on August 9 1932 was plus 10 per cent

Case II.—The second patient that we shall consider is Mr M a thirty nine year-old married Polish laborer who first came to the hospital on February 10 1928 complaining of a swelling of the right side of the neck In 1922 while still living in Poland a large swelling on the left side of the neck was removed Another swelling appeared on the same side in 1926 which disappeared under lamp treatment Two months before entry a lump appeared on the right side of his neck unaccompanied by any pressure symptoms such as cough hoarseness choking feeling or difficulty in swallowing or in breathing He developed a dull pain over right shoulder and clavicle There were no symptoms of hyperthyroidism He slept poorly but his strength was unchanged

Examination showed a well-developed and well nourished man in no pain or distress The pupils were regular equal and reacted normally The left eye showed external strabismus The superficial veins of the neck and upper thorax were prominent. In addition to the scar of the previous operation the neck showed numerous irregular firm confluent masses involving the deeper structures all slightly movable and apparently attached to the thyroid or pharynx. The most prominent masses were situated at the sternal notch and on the right side of the neck, anteriorly There were numerous enlarged cervical and submaxillary lymph nodes which had the same consistency as the other masses All were nontender The heart and lungs were negative and the blood pressure was 130/80 The spleen edge was palpable. The red blood count was 5 102 000 cells per cubic millimeter hemoglobin 90 per cent and white blood count 7500 cells per cubic millimeter The smear showed 10 per cent monocytes and 15 per cent eosinophils. The urine was negative as well as the blood Wassermann reaction The basal metabolic rate was plus 1 per cent.

The roentgen ray revealed a rounded shadow of increased density under the sternum smooth in outline and displacing the trachea to the left There was no evidence of metastases to the bones or lungs The impression of the radiologist was that the substernal mass was thyroid

On February 21st an exploratory dissection of the neck for carcinoma of the thyroid was made by Dr E. P Richardson under ethylene anesthesia A large tumor mass going down into the thorax behind the right sternoclavicular joint was exposed It was infiltrating the overlying muscles and crowded the right lobe of the thyroid inward but left a plane of cleavage between the tumor and the lobe. A portion of muscle was excised for pathologic examination The tumor was undoubtedly malignant but might have

originated from structures other than the thyroid The attempt was made to dissect out the tumor but when it became apparent that it could not be removed without division of the carotid artery and brachial plexus, it was left *in situ*

The patient made an uneventful recovery from the operation Microscopic examination of the tissue removed showed connective tissue filled with hemorrhagic exudate, but no evidence of malignant disease Nevertheless radiation was advised and he received a full erythema dose, 15 x 15 cm field, centering in the region of the thyroid, in three sittings On April 5, 1928, the mass in the neck was noted to be smaller by at least one third, and the chest plate showed almost complete disappearance of the substernal shadow previously seen Consequently the possibility of thymoma or Hodgkin's disease was raised

On October 8, 1928, the patient showed a large nodular, hard, fixed mass in the region of the right lobe and isthmus of the thyroid On the left side, at the angle of the jaw, there was a soft, movable, nontender mass, about 1 × 2 cm The roentgen-ray film revealed a recurrence of the upper mediastinal tumor Consequently he received a full erythema dose, 15 x 15 cm field, deep radiation to the mass in the right side of the neck, followed by half an erythema dose, 10 × 10 cm field, over the manubrium This was done in five sittings in the course of a week. Again the mass in the neck disappeared and a film taken on January 18, 1929, showed the disappearance of the mediastinal tumor as well

On June 10, 1929, patient was examined by Dr F T Hunter who found 2 glands, 3 to 4 cm in diameter at the angle of the left jaw, hard and fixed There were no other masses in the neck or any other glands elsewhere The spleen was enlarged to about 4 cm below costal margin Dr Hunter suggested the diagnosis of lymphoblastoma as a possibility and advised biopsy of a gland in the neck. This could not be done at that time, since the patient refused, and another course of radiation was given He received 533 roentgen units to the left neck, 15 × 15 cm field, followed by a similar dose to the spleen, in four sittings

The patient did not return until January 28, 1932 He gave a history that he had been well until five months previously when the swelling on the right side of the neck recurred There were no masses noticed elsewhere, nor did he have any discomfort from the mass in the neck. Examination showed a small gland below the angle of the left jaw and an indefinite fulness under the sternomastoid on the left The right lobe of the thyroid was occupied by a discretely nodular mass, 3 x 7 cm , extending from the midline outward The skin was not involved The roentgen-ray film showed a marked increase in the substernal shadow which projected well out into the right lung field (Fig 188), and the trachea displaced to the left He was then given a course of radiation of 1200 roentgen units to the right side of the neck and sternum in five divided doses Following this the swelling in the neck diminished in size as well as the substernal mass There remained a good deal of induration in the tissues of the neck, particularly over the thyroid, and several hard, matted glands above each clavicle In addition Dr Hunter found a large, hard spleen, a large mass, 15 × 16 cm in size, in the right abdo

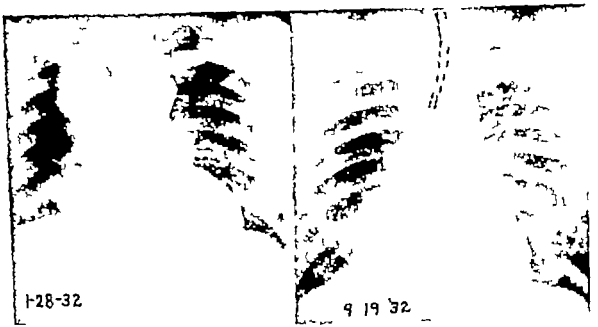

Fig 188 —Changes in the mediastinal mass following radiation therapy in Case II The right plate shows the present status following a series of treatments which began January 28 1932

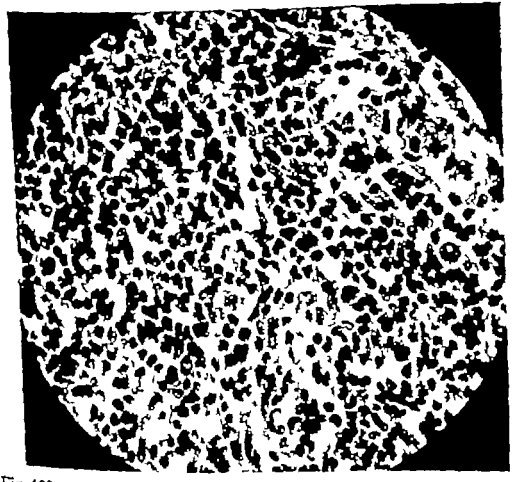

Fig 189 —Photomicrograph showing structure of lymph node in Case II

men and stony hard glands in the right pelvis and groin Consequently the patient was sent into the hospital for biopsy on February 15 1932

A biopsy was done on the right inguinal lymph nodes, removing a small piece of firm grayish tissue The pathologic report by Dr T B Mallory was as follows "Lymph node shows complete obliteration of its architecture, neither sinuses nor lymph follicles being recognizable There is slight to moderate fibrosis and focal collections of eosinophils Scattered irregularly through the tissue are large cells, 2 to 4 times the size of lymphocytes, with vesicular round, lobed, and occasionally multiple nuclei The cytoplasm is slightly acidophilic Occasional mitotic figures are noted in these large cells" (Fig 189)

Diagnosis Lymphoma (Hodgkin's type)

Incidentally the blood Hinton (a precipitin test for syphilis) was found to be weakly positive and antisyphilitic treatment instituted

In view of the findings the patient was given further treatment by radiation of the anterior and posterior abdomen (1380 roentgen units), both groins (810 roentgen units) and both sides of the neck (810 roentgen units) Since then we have witnessed a remarkable change take place At the present time he feels in good health and has no complaints There are no glands or indurated tissue to be felt in the neck The thyroid is not palpable, but there is a question of a small mass in the suprasternal notch which ascends with swallowing Two or three small discrete glands are palpable in each axilla The lungs are clear and there are no masses in the abdomen or groins The chest plate, which is reproduced in Fig 188, shows a marked diminution in the size of the mediastinal shadow observed previously

Undoubtedly he will have recurrences and will require more treatment, but at the present time he is practically free of the disease after a period known to be at least four and a half years and very probably as long as ten years

DISCUSSION

The cases presented illustrate an important type of thyroid disease, usually wrongly diagnosed carcinoma We must bear in mind that it is entirely possible for the thyroid to give rise to lymphoma, alone or in conjunction with other organs, because this process may develop in any organ where lymphoid tissue is present In actual experience, however, we rarely see lymphoma in the thyroid and the number of reported cases is small This is surprising since in exophthalmic goiter focal or diffuse lymphoid infiltration is a feature

The first patient is particularly interesting because the thyroid only was involved There is no evidence at present that any other part of his body is the seat of lymphomatous change In the second case the thyroid was the first organ to be involved (1922), followed six years later by involvement of the cervical glands, and a year after this by enlargement of the spleen

In both instances a diagnosis of carcinoma of the thyroid was made on clinical grounds From the experience with these patients we believe that it is of the utmost importance to consider lymphoma in the differential diagnosis of carcinoma of the thyroid since the response to radiation and the chance of prolonging life are very much better in the former than in the latter The diagnosis, as in these 2 cases, must be settled by examination of a biopsy specimen, although the rapid disappearance of the tumor with radiation should suggest it

The treatment of lymphoma of the thyroid, as demonstrated by these 2 cases, is radiation The roentgen ray is very effective It causes rapid disappearance of the tumors and alleviation of pressure symptoms In Case I the mass in the thyroid was entirely absent at the end of nine months At present, after four years, there is no evidence of recurrence It is not at all unlikely that this represents one of the rare cases with a single lesion, treated before the disease became generalized Consequently he may be completely cured The remarkable disappearance of the thyroid tumor in the neck and in the mediastinum, in Case II, on several occasions under radiation has been most dramatic Although the disease probably has been present for ten years, it has been held in check by radiation for the past four and a half years A similar patient, reported by Krammer,[1] lived for twelve years after surgical removal of part of the thyroid tumor followed by radiation

It follows that in giving prognosis in this type of thyroid lesion we must not be too pessimistic. There is the possibility of complete cure if treated when the disease is still localized, or, at least, the condition may be kept in check for many years

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CLINIC OF DR GEORGE P REYNOLDS

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A CASE OF PSYCHOLOGICAL MALADJUSTMENT IN AN ADULT DUE TO PHYSICAL DEFORMITIES CONTRACTED IN CHILDHOOD

IN the treatment of crippled children, although much attention has been given to the correction of physical deformities, the abnormal psychological reactions which result from being a cripple are often overlooked The case which we are to study today illustrates quite dramatically how the abnormal psychology of a crippled individual may affect his life far more than his physical deformities

In order to give you a clear idea of the psychological reactions which this boy developed it is necessary for me to tell you the outstanding incidents of his life almost from the beginning He is the son of highly intelligent parents and the youngest of five brothers At two years of age he had poliomyelitis, the end result of which was extensive residual paralysis of muscle groups in both legs with shortening and lateral curvature of the spine He had the best of medical care from the beginning of his illness and he soon learned to get about on crutches with great ease and agility By the time he had reached school age he could walk a little without crutches and with their aid he was in the habit of walking a great deal for pleasure So you can see that he had overcome his physical handicap very well, although he was considerably deformed in appearance

He attended a day school for several years and stood well in his studies For that reason his family and teachers never thought of his having any abnormal psychological reactions to his deformity It was noticed that he was habitually dirty and untidy about his personal appearance, but this was attributed

to the aversion of the normal boy to washing and was condoned on the ground that his physical deformity made it difficult for him to keep his clothes and general appearance neat

During his first year at boarding school, however, this untidiness began to amount to an obsession although it was not recognized as such If he was sent away from the table to wash his hands he made repeated attempts to return with them still dirty and when they were finally clean enough to pass muster, it was discovered that he intentionally soiled them immediately after the meal He had a distinct aversion to wearing clean clothes and when forced by threats of severe punishment to put on a fresh shirt he carefully smeared it with dirt at the first opportunity As a result his appearance was habitually so uncouth that it was a matter of general comment even among the boys of his own age But their teasing and all the efforts of a patient and sympathetic housemaster were without effect He had a good brain and was able to reason clearly and logically on almost any other subject, but he was obsessed with a desire to appear dirty and unkempt and all attempts to correct this by means of punishment, persuasion or rewards for cleanliness ended in failure He was naturally shy and reserved and this, combined with his repulsive dirtiness, made him a social outcast He graduated from school five years later and entered college, practically friendless and more uncouth in appearance than ever Under these circumstances it is not surprising that he failed to fit into college life and he resigned at the end of his sophomore year with the situation unchanged except that he was beginning to show a gradually increasing bitterness and hostility toward a world in which he had found no place

In looking for a job he met with failure, for although obviously intelligent and alert mentally, no business man would hire him on account of his slovenly appearance During the next two years he was paymaster of day-laborers for a construction company and did a few odd jobs as a reporter

Treatment—At the end of this time his orthopedist advised an operation for muscle transplantation and fusion of the spine I had been interested in him for years, having always known

him and his family slightly, and it was during his postoperative convalescence that I had an opportunity for the first time to get at the bottom of his psychological tangle I began by dropping into his room every day for a friendly chat It took some time to overcome the hostile attitude which he showed to any visitor, but after the ice was once broken he talked quite freely, especially about his acquaintances in school and college It was obvious from the start that his estimate of an individual was based largely on athletic prowess and that intellectual ability, and social attainment, held no weight with him He said he liked one boy very much because he played on the football team, and spoke of another man that he admired immensely because he almost got his letter in hockey

I also discovered that he was quite interested in psychology and was anxious to discuss a radical book on the subject which he was reading at the time I felt that this presented an excellent means of approaching his own psychological problems, and so, being now on very friendly terms, I deliberately turned the conversation to his future which I knew was puzzling him a great deal He frankly admitted that his previous jobs had been of a very menial nature and had held no prospect of advancement He was beginning to regret that he had not finished college because he felt that the lack of a college degree was responsible for the fact that he had not been able to get what he called "a white collar job" I told him that I did not believe that he could ever get a gentleman's job unless he looked and dressed like a gentleman He immediately retorted with some heat that, if I was leading up to another lecture on cleanliness, I might as well know that he had listened to them all his life and that he was sick of them I replied that I had no intention of lecturing him on cleanliness but, since we had been discussing psychology, I thought it might interest him to know why he *liked* to be dirty Instantly his hostile expression disappeared and it was obvious that my remark had caught his attention

I then told him that I had for years felt sure that his habitual dirtiness was the expression of some abnormal psychological reaction and that I thought our conversations of the past two

weeks had revealed to me the nature of that abnormality I pointed out to him that all our talks had shown quite clearly that the one thing he admired in others was the physical strength that he himself lacked and not the intellectual ability which he had After a little thought he admitted that his ideal was a "superb physical specimen" and that he had not taken into consideration any other qualities I then asked him to consider whether his life-long desire to be dirty, unshaven, and unkempt was not the outward expression of an unconscious longing to appear strong, rough, and manly He thought this over for a few minutes, with an expression of anxious concentration on his face Then he turned to me and said, excitedly, "You're right It is all the result of a He-man Complex My family, the masters at school, and hundreds of others have argued with me all my life about being clean, and I never could see any sense in what they said But I see now that I had a complex which distorted all my reasoning on that subject "

We discussed this a little further and then I left him to think it over by himself The next day his nurse, who knew nothing of the psychological situation, stopped me in the corridor to tell me that he had spent many hours washing, manicuring his nails, and shaving A few days later he left for his home in a large western city, and I heard no more from him for a long time But I learned indirectly that he had procured a good job and was deeply interested in it and that he was much cleaner and more careful about his appearance

About six months later, however, he wrote me one of the most pathetic letters I have ever read In it he said he was trying to find the solution of a very vital problem that was affecting his whole life and he was turning to me because I had been the only person who had been able to help him before He said that he was utterly unable to make friends or even to get on with other people In reviewing his whole life he could only think of three boys and one girl whom he felt he could call friends and with whom he felt at all at ease He thought the reason for this was that he invariably became panic-stricken whenever he had to speak to any one He had tried to analyze

this fear and had come to the conclusion that while it was not entirely physical cowardice there was an element of physical fear in it and he had finally dodged the issue by saying that he was "socially afraid" As an illustration of this he told me of his daily arrival in the office where he was working He said that when he went to hang up his hat each morning he had to face a big, cheerful, attractive young fellow who always smiled and said good morning to him My patient said that he would love to know this man but that he so dreaded their little daily contact that he always tried to sneak in and hang up his hat unnoticed I think this is sufficient to give you a picture of his unhappy state of mind The tragic part of the whole situation was that he believed it was due to some abnormal fear of men in his psychological make-up, and he knew no way of conquering this fear, which both terrified and ashamed him

It is not necessary to go into all the details of the correspondence that followed I think I can summarize it briefly I told him that I should like to give him substitutes for some of the terms he had used in analyzing his own situation I suggested that instead of speaking of "social fear" and "physical cowardice" he think of both as "shyness," and that he regard his "panic" at meeting strangers as nothing more unusual than "embarrassment." I then pointed out that there was a certain amount of shyness in every one's make-up and that this normal quality was inevitably increased in those individuals who were unfortunate enough to be physically deformed I told him that the best way to conquer his shyness and embarrassment was, first, to recognize them as normal qualities, possessed in varying degree by every normal individual, and, second, to try to overcome them by forcing himself to make social contacts

Those of you who have had any experience with the treatment of such situations will realize that much time and a great deal of correspondence was necessary to convince the patient of the simplicity of his problem But I want to emphasize the fact that no more complicated procedure than the simple explanation that I have outlined was necessary to completely straighten out this psychological tangle

This took place three years ago, and although he has since consulted me from time to time on various other problems of human relations, such as sexual continence, it is obvious that his chief psychological problems have been entirely overcome

Discussion—Now let us consider what we may learn from this case It does more than illustrate the development of a maladjustment and the comparatively simple means by which it was treated The whole trend of modern medicine is toward prevention of disease, and there is no type of ailment which can be more successfully prevented than psychological maladjustment Theoretically if treatment were started as soon as the environmental difficulty arose it would be possible to avoid all maladjustments But, from a practical standpoint, there are two reasons why this ideal state of affairs does not exist In the first place, there is an occasional individual whose nervous equilibrium is so easily upset that he cannot be made to adjust himself to even the most ideal environmental situation obtainable in his case Fortunately these unstable personalities are relatively rare A much more important reason for the large numbers of maladjustments found today is the failure to recognize their etiologic factors and to treat the earliest symptoms of the abnormal reaction

In the case we are considering if the boy's dirtiness had been recognized at once as evidence of an obsession due to an abnormal reaction to his physical deformity much of the maladjustment of his adult life might have been avoided But ideal preventive medicine would have instituted treatment much earlier in the case If we study and try to evaluate the many elements which go to make up the complicated environment of modern civilization we find that certain factors are particularly prone to cause maladjustments With this knowledge we are forewarned and when we encounter a situation in which some of these particular factors play a part, we can institute preventive treatment even before the first symptoms of the expected maladjustment begin to appear

It would seem obvious that any physical disability occurring in childhood and leaving permanent deformity must always

be a predisposing cause for a maladjustment The crippled child is deprived of many natural human contacts, such as those gained in competitive sports and childish games He is unable to do what other children do and, since he leads an abnormal existence, he is liable to develop an abnormal reaction to the problems of life

The problem of how to prevent the development of such psychological peculiarities is one that must be dealt with primarily by the parents, but they themselves must have a thorough understanding of it and should, therefore, work under the supervision of a physician who fully comprehends the whole situation and can advise them from time to time It is not a complex psychological problem and the knowledge required to deal with it consists of 90 per cent common sense and 10 per cent ability to recognize the beginning of abnormal reactions But it is a problem that must be dealt with early and continuously throughout childhood and adolescence

It is not possible to outline even general principles of preventive treatment, because naturally these will vary with every individual case. But the most important factor in prevention is the recognition by the physician of the fact that abnormal reactions are to be expected in any crippled child, and that it is his duty to supervise the life of the child so that these reactions may be avoided

Summary —This case is presented in order to illustrate the profound psychological disturbance which may result from mal adjustment in childhood to physical deformities

A boy who was crippled by poliomyelitis at two years of age was not recognized as having any abnormal psychological reactions until he had grown to manhood As a result he was, at the age of twenty three years, uncouth in appearance, practically friendless, and desperately lonely

The treatment of his case consisted simply in an explanation of the origin of his abnormal reactions

This case represents a type to which preventive psychotherapy may be most successfully applied